

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2006N-0229]

Carbinoxamine Products; 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 drug products containing carbinoxamine and persons who cause the manufacture of such products. Numerous drug products containing carbinoxamine are marketed without approved applications and many are inappropriately labeled for use in infants and young children. Drug products containing carbinoxamine are new drugs that require approved applications. One firm has approved applications to market products containing carbinoxamine. In addition, there is information showing that carbinoxamine should not be used in children under 2 years of age. Manufacturers who wish to market carbinoxamine products that do not already have FDA approval must obtain FDA approval of a new drug application (NDA) or an abbreviated new drug application (ANDA). Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of a guidance entitled “Marketed Unapproved Drugs—Compliance Policy Guide.”

DATES: This notice is effective [*insert date of publication in the Federal Register*].

For marketed, unapproved carbinoxamine-containing drug products that have a National Drug Code (NDC) number that is listed with FDA on the effective date of this notice (i.e., “currently marketed products”), however, the agency intends to exercise its enforcement discretion to permit products properly marketed with those NDC numbers a brief period of continued marketing after [*insert date of publication in the **Federal Register***] as follows. Any firm manufacturing such an unapproved drug product containing carbinoxamine that is labeled for use in children less than 2 years of age or marketed as drops for oral administration may not manufacture that product on or after [*insert date 30 days after date of publication in the **Federal Register***]. Any firm manufacturing any other such unapproved drug product containing carbinoxamine may not manufacture that product on or after [*insert date 90 days after date of publication in the **Federal Register***]. Unapproved drug products containing carbinoxamine that are not currently marketed and listed with the agency on the date of this notice must, as of the date of this notice, have approved applications prior to their introduction into interstate commerce.

ADDRESSES: All communications in response to this notice should be identified with Docket No. 2006N–0229 and directed to the appropriate office listed as follows:

Regarding applications under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the act)(21 U.S.C. 355(j)): Office of Generic Drugs (HFD–600), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

Regarding applications under section 505(b) of the act: Division of Pulmonary and Allergy 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.

All other communications: John Loh, Division of New Drugs and Labeling Compliance, Center for Drug Evaluation and Research (HFD–310), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: John Loh, Division of New Drugs and Labeling Compliance, Center for Drug Evaluation and Research (HFD–310), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–8965, e-mail: *John.Loh@FDA.HHS.GOV*.

SUPPLEMENTARY INFORMATION:

I. Background

A. The DESI Review

When initially enacted in 1938, the act required that “new drugs” be approved for safety by FDA before they could legally be sold in interstate commerce. To this end, the act made it the sponsor’s burden to show FDA that its drug was safe through the submission of an NDA. Between 1938 and 1962, if a drug obtained approval, FDA considered drugs that were identical, related, or similar (IRS)¹ to the approved drug to be “covered” by that approval, and allowed those IRS drugs to be marketed without independent approval.

In 1962, Congress amended the act to require that new drugs also be proven effective for their labeled indications, as well as safe. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as safe between 1938 and 1962.

FDA contracted with the National Academy of Science/National Research

¹Section 310.6(b)(1) (21 CFR 310.6(b)(1)) provides: “An identical, related, or similar drug includes other brands, potencies, dosage forms, salts, and esters of the same drug moiety as well as of any drug moiety related in chemical structure or known pharmacological properties.”

Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety. The NAS/NRC reports for these drug products were submitted to FDA in the late 1960s and early 1970s. The agency reviewed and re-evaluated the reports and published its findings in **Federal Register** notices. FDA's administrative implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI). DESI covered the 3,400 products specifically reviewed by the NAS/NRCs, as well as the even larger number of IRS products that entered the market without FDA approval.

All drugs covered by the DESI review are "new drugs" under the act. If FDA's final DESI determination classifies a drug product as ineffective, that drug product and those IRS to it can no longer be marketed and are subject to enforcement action as unapproved new drugs. If FDA's final DESI determination classifies the drug product as effective for its labeled indications, the drug can be marketed provided it is the subject of an application approved for safety and efficacy. Those drug products with NDAs approved before 1962 for safety therefore require approved supplements to their original applications; IRS drug products require an approved NDA or ANDA, as appropriate. Furthermore, labeling for drug products classified as effective may contain only those indications for which the review found the product effective unless the firm marketing the product has received an approval for the additional indication(s).

B. DESI Review of Carbinoxamine Products

Carbinoxamine, often manufactured as carbinoxamine maleate (CM), is a histamine H1 receptor blocking agent (i.e., antihistamine) of the ethanolamine

class.² This class exhibits antihistaminic, anticholinergic, and sedative properties. Certain single-ingredient carbinoxamine products are approved for treatment of various allergy symptoms. Carbinoxamine-containing products are often used for the treatment of colds and cough. However, the approved indications for carbinoxamine do not include treatment of either cold or cough. Carbinoxamine drug products often contain other active ingredients, such as decongestants or antitussives.

CM was initially marketed in the early 1950s. On June 22, 1953, FDA approved an NDA submitted by McNeil Laboratories (McNeil) to market single-ingredient CM in an immediate-release tablet form under the trade name Clistin (NDA 8–915); a tablet in “repeat action” form (an early timed-release technology), marketed as Clistin RA, was approved under the same NDA on June 15, 1954. On June 23, 1953, FDA approved McNeil’s application to market single-ingredient CM in an elixir form under the trade name Clistin (NDA 8–955). On February 5, 1962, the agency approved McNeil’s NDA 9–248 for a combination product, Clistin Expectorant, which contained CM, ammonium chloride, sodium citrate, potassium guaiacolsulfonate, and citric acid.

The Clistin products specifically, and CM generally, were reviewed under DESI. In the **Federal Register** of March 19, 1973 (DESI 6303, 38 FR 7265), FDA announced its conclusions regarding Clistin elixir and Clistin tablets, finding them to be “new drugs” that are effective for the following indications: (1) For the symptomatic treatment of seasonal and perennial allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis due to inhalant allergens and foods; (2) for mild, uncomplicated allergic skin manifestations of urticaria and angioedema; (3) for the amelioration of the severity of allergic reactions to

²Unless a specific salt of carbinoxamine is identified, the term “carbinoxamine” as used in this notice refers to carbinoxamine maleate, carbinoxamine tannate, and any related or similar drug product as described in § 310.6(b)(1) and (b)(2).

blood or plasma in patients with a known history of such reactions; (4) for dermographism; and (5) as therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled. In the **Federal Register** of March 19, 1982 (DESI 6514, 47 FR 11973), FDA announced that Clistin Expectorant was found to lack substantial evidence of effectiveness, because no well-controlled studies documented the effectiveness of its expectorant ingredients and because the combination of an antihistamine and an expectorant was found not to be a rational combination. Accordingly, FDA proposed to withdraw approval of NDA 9–248 (47 FR 11973 at 11974). In the **Federal Register** of April 30, 1982 (DESI 6303, 47 FR 18667), FDA reclassified Clistin RA as lacking substantial evidence of effectiveness because there was no evidence regarding its bioavailability and bioequivalence, as required for a timed-release dosage form of a safe and effective immediate-release drug, and proposed to withdraw approval of NDA 8–915. Because no hearing was requested regarding Clistin Expectorant and no further data were submitted regarding Clistin RA, FDA announced final withdrawal of approval of the NDAs pertaining to these products on May 18, 1982 (47 FR 21301), and July 29, 1983 (48 FR 34514), respectively. These notices also apply to drug products that are IRS to the carbinoxamine products reviewed under DESI.

C. Status of Applications for CM Products

In notices published in the **Federal Register** on April 5, 1985 (50 FR 13661), and March 2, 1994 (59 FR 9989), FDA withdrew approval of the NDAs for Clistin Elixir and Clistin Tablets, respectively, at the request of the application holder because the products were no longer marketed. In response to citizen petitions, FDA published notices in the **Federal Register** of May 21, 1998 (63 FR 27986), and April 10, 2000 (65 FR 18998), confirming that Clistin

CM tablets and elixir, respectively, were not withdrawn from sale for reasons of safety or efficacy and that ANDAs that refer to the products as the listed drug could be approved by the agency.

Mikart, Inc. (Mikart), of Atlanta, GA, submitted ANDAs for single-ingredient CM products in 4-milligram (mg) tablets (ANDA 40-442) and 4 mg/5 milliliter solution form (ANDA 40-458), which were approved by FDA on March 19, 2003, and April 25, 2003, respectively, to treat the indications for which Clistin was found effective in the DESI review. The products are approved as prescription-only drug products. Currently, ANDAs 40-442 and 40-458 are the only approved applications for products containing carbinoxamine.

II. Safety Concerns

The agency is aware of 21 deaths since 1983 in children under 2 years of age associated with carbinoxamine-containing products. However, in most of those incidents, other active ingredients in the drugs or other factors aside from the drug could have been responsible for the death. Therefore, a causative relationship between exposure to carbinoxamine and death in these infants has not been established. Nevertheless, there is scientific support for the proposition that infants and young children may be more susceptible to experiencing drug-related adverse events, in part due to the normal immaturity of their metabolic pathways. Since the safety and efficacy of these drug products have not been studied in infants and young children, FDA is concerned about the risks of these products; the agency is especially concerned about those unapproved CM products that are being promoted for and may be associated with serious and life-threatening adverse outcomes in this vulnerable age group.

In addition, infants and young children administered combination products containing carbinoxamine are at increased risk of suffering an adverse event due to product misidentification or dispensing errors and unintentional overdose. This is due to the existence of multiple strengths, different formulations, and different combinations of active ingredients in marketed, unapproved carbinoxamine-containing products. Moreover, the appropriate dosing of carbinoxamine has not been established for patients under 2 years of age. Dosing suggestions for this age range appear to be extrapolated from adult dosing based on body weight (i.e., mg/kilograms), which is not scientifically supported and can lead to significant dosing errors. Finally, in infants and young children administered these products, parents or caregivers may have difficulty identifying potentially serious or life-threatening adverse events. By the time the serious nature of the event is recognized, it may be too late to successfully intervene.

FDA is also concerned about the potential health risk associated with the use of other unapproved antihistamine and decongestant products in children under 2 years of age. We recognize that there is a similar lack of data regarding use of many of these products in infants and young children, and that variations in formulation and labeling of these products may also lead to errors and adverse events. FDA is evaluating the available scientific data regarding the use of these drugs in infants and young children and assessing appropriate regulatory approaches to best protect the public health. These kinds of products may be high priorities for future FDA enforcement action.

III. Current Status of Carbinoxamine Products

Currently, the Mikart products covered by ANDA 40-442 and ANDA 40-458 are the only products containing carbinoxamine with approved

applications (see section I.C of this document). However, numerous unapproved products containing carbinoxamine are on the market; some are single-ingredient products and others are combination products containing ingredients such as pseudoephedrine, phenylephrine, or dextromethorphan.

As of April 1, 2006, a total of 26 manufacturers had listed with FDA, under section 510(j) of the act (21 U.S.C. 360(j)), a total of 120 prescription drug products containing carbinoxamine. Other unapproved, unlisted carbinoxamine products are also on the market. Various firms distribute these products under various names. In addition to the indications found effective in the DESI review, these products are often used to relieve congestion and other cold symptoms, and some unapproved versions include treatment of cold symptoms as an indication in their labeling.

Many unapproved carbinoxamine products have labeling indicating that they may be used by children under 2 years of age and identify specific dosages for these young children, including some with specific dosages for infants as young as 1 to 3 months. Until recently, the approved carbinoxamine labeling indicated that the product was for use in individuals 1 year of age and older. To address the safety concerns described in this notice, the agency has approved a supplement submitted by Mikart modifying the approved labeling to specifically contraindicate use of the product in children under the age of 2 years. These changes will be reflected in future Mikart labels.

IV. Legal Status

Under DESI 6303, as described previously, a drug product containing CM, alone or in combination with other drugs, is regarded as a new drug (21 U.S.C. 321(p)), and an approved application is required for marketing it. Because DESI drugs are “new drugs,” DESI-effective drugs need approval of an NDA, ANDA,

or the required supplement. (See also *United States v. Sage Pharmaceuticals*, 210 F.3d 475 (5th Cir. 2000) (holding that products containing carbinoxamine are new drugs that require an approved application to be lawfully marketed).)

Thus, the agency intends to take enforcement action against any unapproved drug product that contains CM, whether as its sole active ingredient or in combination with one or more other active ingredients, and anyone who causes the manufacture of such products, as described in this notice. Under § 310.6, this notice also applies to drug products, and those who cause their manufacture, that are marketed without an approved application and that are related or similar to the approved CM products reviewed under DESI 6303, including, but not limited to, products that contain carbinoxamine tannate, alone or in combination with another active ingredient. It is the responsibility of every drug manufacturer to review this notice to determine whether the notice covers any drug product that the person manufactures. Any person may request an opinion of the applicability of this notice to a specific drug product by writing to the Division of New Drugs and Labeling Compliance (see **ADDRESSES**). Requesting such an opinion does not excuse the person from complying with this notice in the time provided herein.

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 firms that are manufacturing products containing carbinoxamine without an approved application that the agency intends to take enforcement action against such products and those who cause them to be manufactured. The lack of approval for a carbinoxamine product can result in seizure, injunction, or other judicial proceeding. Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of a guidance entitled

“Marketed Unapproved Drugs—Compliance Policy Guide” (the Marketed Unapproved Drugs CPG), which describes how the FDA intends to exercise its enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing. 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 manufacturing unapproved products containing carbinoxamine prior to taking enforcement action.

As set forth in this notice, approval of an NDA under section 505(b) of the act, including section 505(b)(2), and 21 CFR 314.50 or an ANDA under section 505(j) of the act and 21 CFR 314.94 is required as a condition for manufacturing all carbinoxamine products. Because the NDAs for Clistin products were withdrawn at the request of the NDA-holder, the Mikart carbinoxamine products as described in ANDAs 40–442 and 40–458 have been designated as the reference listed drug products. Submission of an application does not excuse timely compliance with this notice. Following the effective dates listed in this notice, carbinoxamine products can only be manufactured after obtaining FDA approval.

Consistent with the priorities identified in the Marketed Unapproved Drugs CPG, the agency is taking action at this time against unapproved carbinoxamine products because: (1) Carbinoxamine is a drug with potential safety risks, as described in section II of this document; and (2) the agency has approved an application to market a carbinoxamine-containing product, and thus the continued marketing of unapproved carbinoxamine products is a direct challenge to the drug approval process. 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.

As described in the Marketed Unapproved Drugs CPG, the agency may, at its discretion, exercise its enforcement discretion and identify a period of time during which the agency will not initiate an enforcement action against a *currently marketed* unapproved drug on the grounds that it is an unapproved new drug, to preserve access to medically necessary drugs or ease disruption to affected parties, for instance. The agency notes that there are numerous marketed products that have approved applications or comply with an applicable over-the-counter drug monograph and that are used to treat conditions for which carbinoxamine is commonly used. Based on the facts discussed in this notice, and especially in light of the availability of these products and the special concerns regarding use of carbinoxamine products in children under 2 years of age, FDA intends to implement this notice as follows.

This notice is effective [*insert date of publication in the **Federal Register***]. For marketed, unapproved carbinoxamine-containing products that have an NDC number that is listed with the agency on the effective date of this notice, however, the agency intends to exercise its enforcement discretion to permit products properly marketed with those NDC numbers a period of continued marketing after [*insert date of publication in the **Federal Register***] as follows. Any firm manufacturing such an unapproved drug product containing carbinoxamine that is labeled for use in children less than 2 years of age or marketed as drops for oral administration may not manufacture that product on or after [*insert date 30 days after date of publication in the **Federal Register***]. Any firm manufacturing any other such unapproved drug product

containing carbinoxamine may not manufacture that product on or after [*insert date 90 days after date of publication in the Federal Register*].³ The agency, however, does not intend to exercise its enforcement discretion as outlined in this paragraph if: (1) The manufacturer of an unapproved product covered by this notice is violating other provisions of the act or (2) it appears that a firm, in response to this notice, increases its manufacture of carbinoxamine drug products above its usual production volume during these periods.⁴

Drug manufacturers should be aware that the agency is exercising its enforcement discretion as described above *only* in regard to drug products containing carbinoxamine that are properly marketed under an NDC number listed with the agency on the date of this notice. Unapproved drug products containing carbinoxamine that are not currently marketed and listed with the agency on the date of this notice must, as of the date of this notice, have approved applications prior to their introduction into interstate commerce.

Firms that have discontinued manufacturing products covered by this notice may want to contact FDA to advise us that they are no longer manufacturing those products. Some firms may have previously discontinued the manufacturing of those products without removing them from the listing of their products under section 510(j) of the act. Other firms may discontinue manufacturing 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

³If 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 *United States v. Sage Pharmaceuticals*, 210 F.3d 475, 479–480 (5th Cir. 2000) (permitting the agency to combine all violations of the act in one proceeding, rather than taking action against a firm with multiple violations of the act in “piecemeal fashion”).)

⁴We note that the agency does not intend to take action against, or require removal from the market of, carbinoxamine products already in the drug distribution chain on the dates identified in this notice. Such action or removal may be appropriate for other products in other circumstances.

executive officer, fully identifying the discontinued product, including its NDC number, and stating that the product has been discontinued and will not be marketed again without FDA approval, to the following address: John Loh, Division of New Drugs and Labeling Compliance (see **ADDRESSES**). Firms should also update the listing of their products under section 510(j) of the act to reflect discontinuation of unapproved carbinoxamine products. FDA plans to rely on its existing records, the results of a subsequent inspection, or other available information when it initiates enforcement action.

In addition to discontinuing the manufacture of products that contain carbinoxamine, FDA cautions firms against reformulating their products into carbinoxamine-free unapproved new drugs that are marketed under the same name or substantially the same name (including a new name that contains the old name). In the Marketed Unapproved Drugs CPG, FDA states that it intends to give higher priority to enforcement actions involving unapproved drugs that are reformulated to evade an FDA enforcement action. In addition, reformulated products marketed under a name previously identified with a different active ingredient or combination of active ingredients have the potential to confuse health care practitioners and harm patients. Depending on the circumstances, these products may be considered misbranded under section 502(a) or 502(i) of the act (21 U.S.C. 352(a) and (i)).

FDA notes that 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. Our general approach in dealing with these products in an orderly manner is spelled out in the Marketed Unapproved Drugs CPG. However, this CPG 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.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sections 502 and 505 (21 U.S.C. 352 and 355)) and under authority delegated to the Deputy Commissioner for Policy (21 CFR 5.20).

Dated: June 6, 2006.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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