Questions and Answers about Unapproved Drugs and FDA's Enforcement Action Against Carbinoxamine Products

What actions is FDA taking today?

As part of its ongoing drug safety initiative, the Food and Drug Administration (FDA) today (June 8, 2006) took two important actions to ensure the safety and quality of drugs in the US. First, the agency issued a final guidance document outlining its approach to addressing medicines that are marketed without required FDA approval. Second, in a related action, the FDA is taking enforcement action to stop the manufacturing of unapproved carbinoxamine-containing products because of safety concerns focused on their use in children under 2 years of age.

What is FDA's action concerning carbinoxamine-containing drugs?

FDA has ordered all manufacturers of unapproved products containing carbinoxamine, including carbinoxamine maleate and carbinoxamine tannate, to cease making the products over the next 30 to 90 days. These manufacturers must obtain approval of their products from FDA if they wish to market these products.

Carbinoxamine is a sedating antihistamine. There is one FDA-approved carbinoxamine tablet drug product, and one FDA-approved carbinoxamine oral solution drug product, both of which are manufactured by Mikart, Inc., Atlanta, GA, and approved for the treatment of allergic reactions or their symptoms. They contain carbinoxamine maleate as the active ingredient without any additional active ingredients and are sold only with the following names and formulations:

Palgic Carbinoxamine Maleate Oral Solution, 4mg/5ml,
NDC 0525-6752, PamLab, LLC, Covington, LA;

Carbinox Maleate Solution (Carbinoxamine Maleate Oral Solution; 4mg/5ml),
NDC 54868-5019, Physicians Total Care, Inc., Tulsa, OK;

Palgic Carbinoxamine Maleate Tablets USP, 4mg,
NDC 0525-6748, PamLab, LLC, Covington, LA; and

Palgic Carbinoxamine Maleate Tablets (USP), 4mg,
NDC 54868-5149, Physicians Total Care, Inc., Tulsa, OK.

Numerous unapproved products that contain carbinoxamine, either alone or in combination with other active ingredients, are also on the market. FDA has received 21 reports of death in children under two years of age associated with carbinoxamine-containing drugs. While it is not clear that the carbinoxamine caused these deaths, FDA is concerned about the risks of these unapproved products, some of which are being promoted for infants and young children. Some of the unapproved carbinoxamine

products are labeled for use in children under two years of age, among them many drops and syrups that are specifically labeled for use in children as young as one month of age. Some of these unapproved products are labeled for treatment of cough and cold symptoms, an indication for which carbinoxamine has not been found by FDA to be safe and effective.

Because these drugs are unapproved, FDA has not reviewed their labeling, including the dosing information, warnings and precautions, and indications. Evidence of effectiveness of combination products containing carbinoxamine has not been provided to FDA. The quality of the combination or single-ingredient carbinoxamine products and the processes used in their manufacture have not been independently verified by FDA.

Will carbinoxamine-containing products remain on the market?

Today's action does not affect the approved carbinoxamine product manufactured by Mikart and listed above, which will remain on the market. Companies who are marketing unapproved carbinoxamine products are being ordered to stop making these products until they have obtained FDA approval. However, previously-manufactured products may still be found on pharmacy shelves for a short period of time. Patients should talk to their doctor about whether to use any unapproved carbinoxamine-containing product. Patients and health professionals should carefully consider the medical condition being treated, the patient's previous response to the drug, and the availability of approved alternatives as part of discussing the benefits and risks of this treatment.

What is FDA's action concerning its approach to addressing unapproved, marketed drugs?

FDA is also issuing a final guidance entitled "Marketed Unapproved Drugs--Compliance Policy Guide" designed to make sure that all drugs marketed in the United States, prescription and over-the-counter, have been shown to be safe and effective. For a variety of historical reasons, some drugs, mostly older products, continue to be marketed illegally in the United States without required FDA approval. This guidance clearly articulates FDA's expectation that manufacturers of products requiring FDA approval submit applications to FDA to show that their products are safe and effective. The guidance also outlines the agency's enforcement policies aimed at efficiently and rationally bringing all such drugs into the approval process.

Why is FDA issuing a final guidance on its approach to unapproved, marketed prescription drugs?

FDA is issuing this guidance for reasons directly related to its mission of protecting and advancing the public health. The drug approval process is essential to providing patients and prescribers with the assurance that prescription drugs are marketed based on reliable, scientific data showing that they are safe, effective, well-made, and accurately labeled. The final guidance emphasizes that illegally marketed prescription drugs must obtain FDA approval and explains how the agency will prioritize enforcement actions against illegally marketed drugs to maximize protection of the public health. This final guidance

is based on careful review and consideration of comments received on a previously published draft guidance.

Why is FDA acting now on unapproved drugs?

FDA is committed to ensuring the safety and quality of the nation's drug supply. Today's actions are part of our important role in protecting and advancing the public's health. FDA approval means FDA scientists, physicians, inspectors, and experts have reviewed critical information about a drug and have concluded that the benefits of the drug exceed its risks. Drugs that are not FDA approved may be unsafe, ineffective, of poor quality, or have inadequate labeling. The actions today reflect FDA's broader initiative to provide consumers and the health care community with established and emerging drug safety information so they can make the best possible medical decisions. Although these unapproved drugs have not demonstrated their safety and effectiveness through the drug approval process, health care providers are often unaware of their status and have continued to prescribe them. Their labels do not disclose that they lack approval, and often they are advertised in reputable medical journals or are included in widely used pharmaceutical references such as the Physician's Desk Reference (PDR). The general lack of awareness about the approval status of these drugs, the absence of FDA review of their effectiveness, and the uncertainty about their safety, product quality, and adequacy of labeling, all combine to make it important that unapproved drugs undergo the FDA approval process.

Has the FDA taken previous actions against unapproved drugs that illustrate the importance of the approval process?

Yes. Levothyroxine is a widely prescribed and beneficial drug for thyroid hormone replacement that for years was marketed without FDA approval. FDA received reports of problems with the quality of unapproved levothyroxine products that made it difficult for patients and doctors to predict if a patient was getting a consistent amount of the active ingredient of the drug. In 1997, FDA notified levothyroxine manufacturers that they had three years (later extended to four) to upgrade their manufacturing and submit new drug applications for marketing. This approach avoided shortages for patients and allowed manufacturers time to make the needed improvements, perform testing on the drug, and submit that information in a drug application for FDA approval. Today, all levothyroxine that is marketed must be approved by FDA and meet quality standards.

Because FDA considered levothyroxine to be medically necessary, FDA allowed companies to stay on the market while they were seeking approval and provided ample time for companies to obtain approval.

In other circumstances, FDA may simply issue warning letters ordering the immediate cessation of illegal drug manufacturing. As explained in the guidance, the decision about how to proceed will be made on a case-by-case basis.

What drugs will FDA take off the market?

FDA's new Compliance Policy Guide outlines a prioritized enforcement approach encouraging companies currently manufacturing drugs without required FDA approval to

comply with the drug approval process and ensure the safety and efficacy of their marketed products. If companies do not do so, FDA may take enforcement action. The highest priorities for enforcement action will continue to be drugs with potential safety risks, drugs that lack evidence of effectiveness, and health fraud drugs. FDA will proceed on a case-by-case basis with these priorities in mind, with every effort made to avoid adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the drug supply.

How does FDA intend to handle situations where there is an approved and unapproved version of the same drug?

In deciding whether, and in what manner, to take enforcement action against an unapproved drug, FDA intends to consider, among other factors, whether there is also an approved drug available to serve consumers who need the drug. Allowing continued marketing of unapproved drugs that compete against approved counterparts challenges the integrity of the drug approval system that is designed to avoid the risks associated with potentially unsafe and ineffective drugs, and puts companies that comply with the law at a disadvantage. Allowing continued marketing of these unapproved drugs also undermines the incentives needed to conduct the scientific studies to determine the safety and effectiveness of drugs, which benefits the public health.

Is FDA required to publish a Federal Register notice before taking any action against any unapproved drug?

No. FDA may take action against unapproved new drugs without first publishing its intentions in the Federal Register. However, FDA will continue to be mindful of the effects of its action on consumers and health professionals and set its priorities according to their public health impact.

For further information, please see FDA's Unapproved Drugs Web Page, located at http://www.fda.gov/cder/drug/unapproved_drugs/default.htm