October 22, 2018

Dear CEO or President:

This letter concerns unapproved prescription drug products containing local anesthetics, which are now or have previously been manufactured, repackaged, relabeled, or distributed by your firm. Your firm is receiving this letter based on drug registration and listing information provided to the Food and Drug Administration (FDA or Agency). As described below, your firm should take prompt action to relabel or discontinue the distribution and sale of your prescription drug product(s) containing local anesthetics based on evidence that these products pose a serious and potentially fatal risk of methemoglobinemia.

Background

Unapproved prescription drug products containing local anesthetics are marketed in a variety of dosage forms, including gels, dentifrices, sprays, ointments, and solutions. Benzocaine, lidocaine, and tetracaine are examples of active ingredients found in several types of prescription drug products containing local anesthetics labeled for, among other uses, the temporary relief of pain.

Some of these unapproved prescription drug products containing local anesthetics may be subject to an ongoing Drug Efficacy Study Implementation (DESI) proceeding. The Agency has a longstanding policy under which it generally has refrained from acting against marketed unapproved drug products that are subject to an ongoing DESI proceeding. However, as stated in FDA's Guidance for FDA Staff and Industry, Marketed Unapproved Drugs—Compliance Policy Guide, Section 440.100 (September 19, 2011), unapproved prescription drug products with potential safety risks are an enforcement priority for the Agency.[1]

Association Between Local Anesthetics and Methemoglobinemia

Methemoglobinemia is a serious and potentially life-threatening condition where the amount of oxygen carried through the blood stream is greatly reduced.

The Agency has conducted multiple reviews of the FDA Adverse Event Reporting System

[1] See Guidance for FDA Staff and Industry, Marketed Unapproved Drugs—Compliance Policy Guide, Section 440.100 (September 19, 2011), p. 4, *available at* https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070290.pdf.

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(FAERS) and published literature to identify and evaluate cases of methemoglobinemia associated with the use of drug products containing local anesthetics. Cases of methemoglobinemia have been, and continue to be, reported for "caine" local anesthetics, both prescription and over-the-counter (OTC). For example, based on its reviews, the Agency estimates that more than 400 cases of benzocaine-associated methemoglobinemia occurring in the United States have been reported to FAERS and published in the medical literature since 1971. Recently conducted searches of the FAERS database also have demonstrated that cases of methemoglobinemia have been, and continue to be, reported for non-benzocaine local anesthetics, including bupivacaine, lidocaine, prilocaine, and tetracaine.

Requested Labeling Revision

FDA has issued several communications to consumers, health care providers, and manufacturers regarding the risks of methemoglobinemia associated with benzocaine products used for medical procedures and OTC indications.[2] As evidence of this association continued to mount, the Center for Drug Evaluation and Research (CDER) intensified its efforts to understand methemoglobinemia risk associated with local anesthetics, both prescription and OTC. As part of this effort, CDER conducted a comparison of labeling about methemoglobinemia across the class of "caine" local anesthetics and found substantial inconsistencies in communicating the risk of methemoglobinemia associated with these products. Based on the safety concerns described above,[3] FDA believes that the prescribing information for prescription drug products containing local anesthetics should include the following language:

WARNINGS AND PRECAUTIONS

Methemoglobinemia

Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary

[2] See, e.g., "FDA Drug Safety Communication: FDA continues to receive reports of a rare, but serious and potentially fatal adverse effect with the use of benzocaine sprays for medical procedures" (April 7, 2011), *available at* https://www.fda.gov/Drugs/DrugSafety/ucm250040.htm; and "FDA Drug Safety Communication: Reports of a rare, but serious and potentially fatal adverse effect with the use of over-the-counter (OTC) benzocaine gels and liquids applied to the gums or mouth" (April 7, 2011), *available at* https://www.fda.gov/Drugs/DrugSafety/ucm250024.htm.

[3] In May 2018, FDA required manufacturers of FDA-approved prescription local anesthetics to standardize warning information about the risk of methemoglobinemia in product labeling across this class of products. Manufacturers of approved, prescription local anesthetics were given 30 days to reply to the Agency's letter regarding these new Safety Labeling Changes. See https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm608325.htm

compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs and symptoms of methemoglobinemia may occur immediately or may be delayed some hours after exposure and are characterized by a cyanotic skin discoloration and abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue [TRADENAME] and any other oxidizing agents. Depending on the severity of the symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. More severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

DRUG INTERACTIONS

Patients that are administered local anesthetics may be at increased risk of developing methemoglobinemia when concurrently exposed to the following oxidizing agents:

Class	Examples
Nitrates/Nitrites	nitroglycerin, nitroprusside, nitric oxide, nitrous oxide
Local anesthetics	benzocaine, lidocaine, bupivacaine, mepivacaine, tetracaine, prilocaine, procaine, articaine, ropivacaine
Antineoplastic agents	cyclophosphamide, flutamide, rasburicase, ifosfamide, hydroxyurea
Antibiotics	dapsone, sulfonamides, nitrofurantoin, para-aminosalicylic acid
Antimalarials	chloroquine, primaquine
Anticonvulsants	phenytoin, sodium valproate, phenobarbital
Other drugs	acetaminophen, metoclopramide, sulfa drugs (i.e., sulfasalazine), quinine

PATIENT COUNSELING INFORMATION

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to stop use and seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath;

lightheadedness; or fatigue.

Conclusion

Based on the currently available information about the risk of methemoglobinemia described above, and consistent with the Agency's risk-based approach to marketed unapproved drugs, FDA no longer intends to extend its enforcement discretion policy to marketed unapproved prescription drug products containing local anesthetics, unless they mitigate the risk of methemoglobinemia by addressing this risk in the labeling. The Agency intends to continue its longstanding policy with respect to the marketing of products subject to a pending DESI proceeding (including products that are identical, related, or similar to those subject to a pending DESI proceeding),[4] so long as the labeling of any such unapproved prescription local anesthetic drug products contains language in the labeling addressing and mitigating the risk of methemoglobinemia.

FDA continues to review information regarding the risk of methemoglobinemia posed by drug products containing local anesthetics and may consider additional regulatory action in the future to address this serious health risk.[5]

Please note that all firms are required to electronically update the listing of their products under section 510(j) of the Federal Food, Drug, and Cosmetic Act if there is any material change in any of the information previously submitted in the listing. Specifically, registrants of establishments that manufacture, repack, relabel, or salvage prescription drugs must review and update their drug listing information each June and December.[6] Registrants that discontinue the marketing of their products must submit a delisting for each product's National Drug Code. Registrants must submit any material changes in the labeling of their products and any other information previously submitted pursuant to 21 C.F.R. § 207.49 or other relevant sections of part 207.[7] Registrants are encouraged to update listing information at the time of any change affecting information previously submitted.[8]

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[4] See 21 C.F.R. § 310.6 ("Applicability of 'new drug' or safety or effectiveness findings in drug efficacy study implementation notices and notices of opportunity for hearing to identical, related, and similar drug products").

[5] The Agency has taken recent action with respect to OTC oral healthcare drug products containing benzocaine as well as approved prescription drug products containing local anesthetics. For additional information, see "Risk of serious and potentially fatal blood disorder prompts FDA action on oral over-the-counter benzocaine products used for teething and mouth pain and prescription local anesthetics" (May 23, 2018), *available at* https://www.fda.gov/Drugs/DrugSafety/ucm608265.htm.

[6] 21 C.F. R. § 207.57(b).

[7] Id.

[8] Id. at § 207.57(c).

If you have any questions about the contents of this letter, please contact CDEROUDLCPMTRACK@CDER.FDA.GOV.

Sincerely,

Carolyn Becker
Director
Office of Unapproved Drugs and Labeling Compliance
Office of Compliance
Center for Drug Evaluation and Research