Dear Healthcare Professionals,

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

Your attention is drawn to the US Food and Drug Administration’s (FDA) announcement that FDA is warning that over-the-counter (OTC) oral drug products containing benzocaine should not be used to treat infants and children younger than 2 years. FDA is also warning that benzocaine oral drug products should only be used in adults and children 2 years and older if they contain certain warnings on the drug label. These products carry serious risks and provide little to no benefits for treating oral pain, including sore gums in infants due to teething. Benzocaine, a local anesthetic, can cause a condition in which the amount of oxygen carried through the blood is greatly reduced. This condition, called methemoglobinemia, can be life-threatening and result in death.

Due to the significant safety risk of methemoglobinemia, FDA has urged manufacturers that they should stop marketing OTC oral drug products for treating teething in infants and children younger than 2 years. If companies do not comply, FDA will take action to remove these products from the market. FDA has also urged manufacturers of OTC oral drug products containing benzocaine for adults and children 2 years and older to make the following changes to the labels of their products:

- Adding a warning about methemoglobinemia;
- Adding contraindications, FDA’s strongest warnings, directing parents and caregivers not to use the product for teething and not to use in infants and children younger than 2 years; and
- Revising the directions to direct parents and caregivers not to use the product in infants and children younger than 2 years.

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Benzocaine is a local anesthetic contained in some OTC products for the temporary relief of pain due to minor irritation, soreness, or injury of the mouth and throat. Benzocaine products are marketed as gels, sprays, ointments, solutions, and lozenges.

FDA is also requiring a standardized methemoglobinemia warning to be included in the prescribing information of all prescription local anesthetics. Prescription local anesthetics include articaine, bupivacaine, chloroprocaine, lidocaine, mepivacaine, prilocaine, ropivacaine, and tetracaine.

Consumers using benzocaine products to treat mouth pain should seek medical attention immediately for signs and symptoms of methemoglobinemia. These include pale, gray or blue-colored skin, lips, and nail beds; shortness of breath; fatigue; confusion; headache; lightheadedness; and fast heart rate. Signs and symptoms of methemoglobinemia may appear within minutes to one to two hours after using benzocaine. Symptoms may occur after using benzocaine for the first time, as well as after prior uses.

Healthcare professionals should warn patients of the possibility of methemoglobinemia and advise them of the signs and symptoms when recommending or prescribing local anesthetic products. Some patients are at greater risk for complications related to methemoglobinemia. This includes those with breathing problems such as asthma, bronchitis, or emphysema; heart disease, and the elderly. Healthcare professionals using local anesthetics during medical procedures should take steps to minimize the risk for methemoglobinemia. These include monitoring patients for signs and symptoms suggestive of methemoglobinemia; using co-oximetry when possible; and having resuscitation equipment and medications readily available, including methylene blue.

FDA has been closely monitoring the risk of methemoglobinemia with the use of OTC and prescription local anesthetics and previously communicated about this risk in 2014, 2011, and 2006. FDA estimates that more than 400 cases of benzocaine-associated methemoglobinemia have been reported to FDA or published in the medical literature since 1971. There are likely additional cases about which FDA is unaware.

As part of FDA’s continued monitoring of this safety risk, FDA recently evaluated 119 cases of benzocaine-associated methemoglobinemia reported to FDA and identified in the medical literature in the 8½ years between Feb 2009 and Oct 2017. FDA has continued to receive cases even after its 2014 communication. Most of the 119 cases were serious and required treatment. Twenty-two cases occurred in patients younger than 18 years, and 11 of these were in children younger than 2 years. Four patients died among the 119 patients, including one infant. FDA also conducted a study comparing the relative ability of the two local anesthetics benzocaine and lidocaine to make methemoglobin. The study showed that benzocaine generated much more methemoglobin than lidocaine in a red blood cell model.

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Please refer to the following website in FDA for details:

In Hong Kong, there are 14 registered pharmaceutical products containing benzocaine. Amongst these 14 products, 9 products are in oral preparation, including 2 products which are oral/dental gels and 7 products which are lozenges. Regarding the prescription local anesthetics listed in the above FDA’s announcement, there are registered prescription products in Hong Kong containing articaine (7 products), bupivacaine (7 products)/levobupivacaine (4 products), lidocaine (81 products), mepivacaine (3 products), ropivacaine (3 products) and tetracaine (1 product). Other registered prescription products containing local anesthetics include cocaine (2 products), procaine (1 product) and cinchocaine (9 products). So far, the Department of Health (DH) has received 5 cases of adverse drug reaction related to lidocaine and 1 case related to prilocaine, but these cases were not related to methemoglobinemia.

News related to risk of methemoglobinemia of benzocaine was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 8 Apr 2011, with the latest update posted on 10 Apr 2012. Letters to inform local healthcare professionals were issued by DH on 8 Apr 2011 and 10 Apr 2012. In Jun 2011 and Apr 2013, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided that the labelling of benzocaine products for topical oral use and all benzocaine products except lozenges preparation should contain information on the risk of methemoglobinemia respectively. In light of the above FDA’s updated recommendations, the matter will be further discussed by the Registration Committee of the Pharmacy and Poisons Board. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under “ADR Reporting”: http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office’s website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Joseph LEE)
for Assistant Director (Drug)

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