FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
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DRAFT QUESTIONS

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1. **DISCUSS:** The current pharmacokinetic standard for approval of naloxone products for use in the community requires demonstration of naloxone levels comparable to or greater than the levels achieved with the approved starting dose of 0.4 mg of naloxone injection administered by one of the approved, labeled routes of administration in adults [intravenous (IV), intramuscular (IM), or subcutaneous injection (SQ)], with a minimum of two doses packaged together.

    a. Discuss whether matching or exceeding the naloxone exposure from a 0.4 mg injection of naloxone represents a high enough naloxone exposure to remain the basis for approval of novel products. Please take into consideration the variety of opioids that may be involved in an overdose in the community including: prescribed opioids vs. illicit opioids (heroin, heroin laced with fentanyl or carfentanil); partial agonists vs. full agonists.

    b. If you think a higher minimum naloxone level is more appropriate as the basis for approval of new products intended for use in the community, describe the target naloxone level and the rationale for this approach.

    c. In controlled settings with trained health care providers and adequate ventilatory support, naloxone can be titrated to reverse an opioid overdose and minimize the risk for precipitating an acute withdrawal syndrome in an opioid-tolerant individual. In the community, trained health care providers and adequate ventilatory support may not be available, and naloxone may be administered by a layperson relying solely on the instructions for use that accompanies the naloxone product. In this latter setting, there is a 5- to 10-minute window before hypoxic injury becomes irreversible. Discuss how to balance the need for rapid reversal of an opioid overdose with the risk for precipitating an acute opioid withdrawal syndrome when selecting the minimum naloxone exposure that forms the basis for approval of novel products.

DRAFT QUESTIONS (cont.)

2. **DISCUSS:** The approved dosing for known or suspected opioid overdose in adults is as follows: An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of opioid induced or partial opioid induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

   The approved dosing for known or suspected overdose in the pediatric population is as follows: The usual initial dose in pediatric patients is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered.

   The past AAP recommendations for naloxone dosing in infants and children are as follows: 0.1 mg/kg for infants and children from birth to 5 years of age or 20 kg of body weight. Children older than 5 years of age or weighing more than 20 kg may be given 2.0 mg. These doses may be repeated as needed to maintain opiate reversal.

   a. Discuss whether the minimum exposure criterion (naloxone levels comparable to or greater than the levels achieved with 0.4 mg of naloxone injection) is appropriate for managing opioid overdose in children. If you do not think the standard is appropriate for children, discuss the criteria that should be used for naloxone products intended for use in children. Discuss whether the recommended criteria are suitable for use in adults.

   b. If different standards and resultant naloxone products are recommended for adults and children, one concern is that the presence of more than one naloxone product in a home may result in confusion about which product to administer in an emergency setting. Discuss how the risk of medication errors can be reduced in this setting.

   c. Discuss the need (if any) for PK and safety information in pediatric patients, depending on the route of administration and inactive ingredients, and any recommendations for how these data can be obtained.

DRAFT QUESTIONS (cont.)

3. **VOTE:** Is the pharmacokinetic standard based on 0.4 mg of naloxone given by an approved route (IV, IM, SQ) appropriate for approval of naloxone products for use in the community or are higher doses and/or exposures required?

    a. Continue with the current minimum standard of comparable or greater exposure compared to 0.4 mg of naloxone injection

    b. Increase the minimum acceptable naloxone exposure to that comparable to or greater than a higher dose of naloxone injection

4. **VOTE:** Should there be different minimum standards used to support the approval of products intended for use in adults and in children?

5. **DISCUSS:** Some Sponsors have proposed marketing more than one dose strength for their naloxone products intended for use in the community. When these strengths all meet or exceed the minimum naloxone exposure level set forth by the Agency, it is unclear what factors to describe in labeling to assist health care providers in making a decision to prescribe one dose strength over another.

    Discuss what, if any, data Sponsors should provide to support the approval of more than one dose strength for any one naloxone product, and that can provide guidance to assist clinicians in dose selection.

6. **DISCUSS:** As part of the standard for approval, naloxone products intended for use in the community have Instructions for Use (IFU) suitable for use by laypersons as supported by human factors studies and additional training is not required.

    a. Discuss whether there is a role for new naloxone products intended for use in the community that requires training beyond the IFU.

    b. Discuss the characteristics that should be considered for the study population enrolled in human factor studies of novel naloxone products. In particular, discuss the appropriate age range of study participants and whether the studies should specifically enroll adolescents, and if so, down to what minimum age. Also discuss whether these studies should specifically enroll caregivers of infants and children.