DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 009470

LABELING ORDER

Fresenius Kabi USA LLC
Three Corporate Drive
Lake Zurich, IL 60047

Attention: Deryl Ann Richburg
Senior Regulatory Affairs Specialist

Dear Ms. Richburg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xylocaine Viscous (lidocaine HCl) Solution.

On June 25, 2014, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Xylocaine Viscous (lidocaine HCl) Solution to address the risk of fatal and life-threatening adverse events related to accidental ingestion or overdose of 2% viscous lidocaine solution by infants or young children. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

We received neither a supplement proposing labeling changes nor a rebuttal statement within the allotted 30 days. You have therefore forfeited the discussion period.

On July 11, 2014, FDA received your request for withdrawal of approval of your NDA for Xylocaine Viscous (lidocaine HCl) Solution. During a phone call on July 23, 2014, you indicated that you believe that a labeling change to address the risks above is not warranted because you are not currently marketing the drug and have decided to withdraw this application. However, as explained in the June 25, 2014, safety labeling change notification letter, requirements under section 505(o)(4) of the Act apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug under an NDA, unless approval of your application has been withdrawn in the Federal Register. Additionally, your drug is currently listed as “active” in the Orange Book. Therefore, even though you are not currently marketing your product, because your drug is considered to be currently marketed and the application has not been withdrawn, you are required to comply with the safety labeling change requirements in section 505(o)(4) of the Act.

Under the authority of Section 505(o)(4)(E), we are ordering you to make all of the changes in the labeling listed in the June 25, 2014, letter (attached).

Pursuant to Section 505(o)(4)(E), a changes being effected (CBE) supplement containing all of the changes to the labeling that are listed in the June 25, 2014, letter must be received by FDA by August 15, 2014, for Xylocaine Viscous (lidocaine HCl) Solution.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

Alternatively, by August 5, 2014, you may appeal this Order using the Agency's established formal dispute resolution process as described in 21 CFR 10.75 and the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level." http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM343101.pdf. The appeal should be submitted as a correspondence to your NDA referenced above. Identify the submission as "**Formal Dispute Resolution Request**" both on the cover letter and on the outside envelope. A copy of the submission should be sent to:

Khushboo Sharma
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Office of New Drugs
White Oak Complex, Building 22, Room 6468
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, to expedite coordination of any such appeal, a copy of the submission should also be sent to:

Mark Liberatore
Safety Regulatory Project Manager
Food and Drug Administration
Division of Anesthesia, Analgesia, and Addiction Products
Building 22, Room 3168
10903 New Hampshire Avenue
Silver Spring, MD 20993

Refer to the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level" for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Khushboo Sharma, CDER Formal Dispute Resolution Project Manager, at (301) 796-1270. Appeals received by the Agency later than August 5, 2014, will not be entertained.

Failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. 333(f)(4), in the amount of up to $250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your

product to be misbranded under section 502(z) of the Act, 21 U.S.C. 352(z), which could subject you to additional enforcement actions, included but not limited to seizure of your product and injunction.

If you have any questions, call Mark Liberatore, Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Safety Labeling Change Notification Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 009470

SAFETY LABELING CHANGE NOTIFICATION

Fresenius Kabi USA LLC
Three Corporate Drive
Lake Zurich, IL 60047

Attention: Deryl Ann Richburg
Senior Regulatory Affairs Specialist

Dear Ms. Richburg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xylocaine Viscous (lidocaine HCl) Solution.

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to make safety related label changes based upon new safety information that becomes available after approval of the drug or biological product. Since Xylocaine Viscous (lidocaine HCl) Solution was approved on September 2, 1954, we have become aware of fatal and life-threatening adverse events related to accidental ingestion or overdose of 2% viscous lidocaine solution by infants or young children. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for Xylocaine Viscous Solution as follows:

The strikethroughs indicate text that should be deleted, and underlining indicates text that should be inserted.

BOXED WARNING

Life-threatening and fatal events in infants and young children

Postmarketing cases of seizures, cardiopulmonary arrest, and death in patients under the age of 3 years have been reported with use of Xylocaine 2% Viscous Solution when it was not administered in strict adherence to the dosing and administration recommendations. In the setting of teething pain, Xylocaine 2% Viscous Solution should generally not be used. For other conditions, the use of the product in patients less than 3 years of age should be limited to those situations where safer alternatives are not available or have been tried but failed.

To decrease the risk of serious adverse events with use of Xylocaine 2% Viscous Solution, instruct caregivers to strictly adhere to the prescribed dose and frequency of administration and store the prescription bottle safely out of reach of children.

WARNINGS

EXCESSIVE DOSAGE, OR SHORT INTERVALS BETWEEN DOSES, CAN RESULT IN HIGH PLASMA LEVELS AND SERIOUS ADVERSE EFFECTS. PATIENTS SHOULD BE INSTRUCTED TO STRICTLY ADHERE TO THE RECOMMENDED DOSAGE AND ADMINISTRATION GUIDELINES AS SET FORTH IN THIS PACKAGE INSERT.

THE MANAGEMENT OF SERIOUS ADVERSE REACTIONS MAY REQUIRE THE USE OF RESUSCITATIVE EQUIPMENT, OXYGEN, AND OTHER RESUSCITATIVE DRUGS.

Xylocaine 2% Viscous Solution should be used with extreme caution if the mucosa in the area of application has been traumatized, since under such conditions there is the potential for rapid systemic absorption.

Life-threatening and fatal events in infants and young children

Postmarketing cases of seizures, cardiopulmonary arrest, and death in patients under the age of 3 years have been reported with use of Xylocaine 2% Viscous Solution when it was not administered in strict adherence to the dosing and administration recommendations. In the setting of teething pain, Xylocaine 2% Viscous Solution should generally not be used. For other conditions, the use of the product in patients less than 3 years of age should be limited to those situations where safer alternatives are not available or have been tried but failed.

PRECAUTIONS

Information for Patients
(NOTE TO SPONSOR: this section of "Information for Patients" should precede the existing labeling in this section)

Parents and caregivers should be cautioned about the following:

• For patients under 3 years of age, special care must be given to accurately measuring the prescribed dose and not administering the product more often than prescribed.
• To ensure accuracy, we recommend you use a measuring device to carefully measure the correct volume.
• The product should only be used for the prescribed indication.
• To reduce the risk of accidental ingestion, the product container should be tightly closed and the product should be stored well out of reach of all children immediately after each use.

• If the patient shows signs of systemic toxicity (e.g., lethargy, shallow breathing, seizure activity) emergency medical attention should be sought immediately and no additional product should be administered.
• Unused product should be discarded in a manner that prevents possible exposure to children and pets.

DOSAGE AND ADMINISTRATION
Pediatric:
Care must be taken to ensure correct dosage in all pediatric patients as there have been cases of overdose due to inappropriate dosing.

It is difficult to recommend a maximum dose of any drug for children since this varies as a function of age and weight. For children over 3 years of age who have a normal lean body mass and normal body development, the maximum dose is determined by the child's weight or age. For example: in a child of 5 years weighing 50 lbs., the dose of lidocaine hydrochloride should not exceed 75-100 mg (b) (4) (3.7 to 5 mL of Xylocaine 2% Viscous Solution).

For infants, and in children under 3 years of age, (b) (4) the solution should be accurately measured and no more than 1.2 mL be applied to the immediate area with a cotton-tipped applicator. (b) (4) (b) (4) Wait at least 3 hours before giving the next dose; (b) (4) (b) (4) a maximum of four doses may be given in a 12-hour period. Xylocaine 2% Viscous Solution should only be used if the underlying condition requires treatment with a volume of product that is less than or equal to 1.2 mL.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS).

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in **30 days** may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED)."

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

If you do not submit electronically, please send 5 copies of the submission.

If you have any questions, call Diana Walker PhD, Sr. Regulatory Health Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUDITH A RACOOSIN
06/25/2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
07/31/2014