DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDAs 088184 (25 mg/mL)
088185(50 mg/mL)

LABELING ORDER

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

Attention: Grace Burbulys
Senior Regulatory Specialist

Dear Ms. Burbulys:

Please refer to your Abbreviated New Drug Applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Hydroxyzine Hydrochloride Injection USP, 25 mg/mL and 50 mg/mL.

On April 9, 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 Hydroxyzine Hydrochloride Injection, USP to address the risk of an association between the use of Hydroxyzine Hydrochloride Injection, USP and severe injection site reactions. 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.

On May 12, 2014, FDA received your email detailing the reasons why you believe a labeling change to address the risk listed above is not warranted for Hydroxyzine Hydrochloride Injection, USP; specifically that you plan to withdraw this application. However, as explained in the April 9, 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and ANDAs without a currently marketed reference listed drug under an NDA, unless approval of your application has been withdrawn in the Federal Register. Therefore, even if you are not currently marketing your product, because your application has not been withdrawn, you are required to comply with the safety labeling change requirements in section 505(o)(4) of the Act.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) of the FDCA, we are ordering you to make all of the changes in the labeling listed in the April 9, 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 April 9, 2014, letter must be received by FDA by June 18, 2014, for Hydroxyzine Hydrochloride Injection, USP.

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 June 8, 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 ANDA 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:

Amy Bertha
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Building 22, Room 6465
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:

Carrie Lemley
Labeling Project Manager
Office of Generic Drugs
Food and Drug Administration
Room 3660, Bldg. 757
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 Amy Bertha, CDER Formal Dispute Resolution Project Manager, at (301) 796-1647. Appeals received by the Agency later than June 8, 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 Jasmeet Kalsi, Regulatory Project Manager, at (240) 276-8518.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

ENCLOSURE(S): Safety Labeling Change Notification Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDAs 087329 (25 mg/mL and 50 mg/mL)
088184 (25 mg/mL)
088185(50 mg/mL)

SAFETY LABELING CHANGE NOTIFICATION

Fresenius Kabi USA, LLC
Attention: Jenna Holm
Three Corporate Drive
Lake Zurich, IL 60047

Dear Madam:

Please refer to your Abbreviated New Drug Applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Hydroxyzine Hydrochloride Injection USP, 25 mg/mL and 50 mg/mL.

Section 505(o)(4) of the (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 Hydroxyzine Hydrochloride Injection, USP was approved on August 11, 1981, March 31, 1983, and March 31, 1983, respectively, we have become aware of postmarketing reports in the FDA Adverse Event Reporting System (FAERS) and the medical literature that suggest an association between the use of Hydroxyzine Hydrochloride Injection, USP and severe injection site reactions. 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 Hydroxyzine Hydrochloride Injection, USP as follows:

Revise the **WARNINGS** section of the package insert to add the below information as the first paragraph in the WARNINGS section.

WARNINGS

Tissue damage: Intramuscular hydroxyzine hydrochloride may result in severe injection site reactions (including extensive tissue damage, necrosis and gangrene) requiring surgical intervention (including debridement, skin grafting and amputation).

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 have any questions, call Jasmeet Kalsi, Regulatory Project Manager, at (240) 276-8518.

Sincerely,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
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/

ROBERT L WEST
04/09/2014
Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

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

/s/

CARRIE L LEMLEY
06/03/2014