DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 040805

LABELING ORDER

Hetero USA, Inc.
U.S. Agent for HETERO LABS LIMITED UNIT- III
1035 Centennial Avenue
Piscataway, NJ 08854
Attention: Soma Raju
Director-Regulatory Affairs

Dear Dr. Raju:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Hydroxyzine Hydrochloride Tablets USP, 10 mg, 25 mg, and 50 mg.

On August 11, 2016, 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 products related to the association with acute generalized exanthematous pustulosis (AGEP). 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.

Further reference is made to the email sent by Carol Lee on October 5, 2016, notifying you that the labeling language proposed in the August 11, 2016 letter has been revised.

Additionally, a final reminder to submit updated labeling was sent to you via email by Kyle Snyder on October 14, 2016. You were also advised that 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and ANDAs without a currently marketed reference listed drug under an NDA, unless approval of your application has been withdrawn in the Federal Register. Therefore, even if you are not currently marketing your product, because your application has not been withdrawn, you are required to comply with the safety labeling change requirements in section 505(o)(4) of the Act.

As of the date of this letter, the Agency has received no correspondence from you.

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 August 11, 2016 letter and October 5, 2016 email (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 August 11, 2016 letter and October 5, 2016 email must be received by FDA by December 1, 2016, for Hydroxyzine Hydrochloride Tablets, 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 November 16, 2016, 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:

Hyon J. Kim
Labeling Project Manager
Office of Generic Drugs
Food and Drug Administration
Bldg. 75, Room 3625A
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 November 16, 2016, 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, contact Hyon J. Kim, Labeling Project Manager, at (240) 402-7766 or Hyon.Kim@fda.hhs.gov.

Sincerely,

Kathleen Uhl, M.D.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
Safety Labeling Change Notification Letter
Email with Revised Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 040805

SAFETY LABELING CHANGE NOTIFICATION

Hetero USA, Inc.
U.S. Agent for Hetero Labs Limited Unit-III
1035 Centennial Avenue
Piscataway, NJ 08854

Attention: Soma Raju
Director, Regulatory Affairs

Dear Dr. Raju:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Hydroxyzine Hydrochloride Tablets USP, 10 mg, 25 mg, and 50 mg.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved new drug applications (NDAs) and biological license applications (BLAs) to make safety related labeling changes based upon "new safety information," as defined in section 505-1(b)(3) of the FDCA, about which FDA becomes aware after approval of the drug or biological product. 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.

Since Hydroxyzine Hydrochloride Tablets, USP, was originally approved, we have identified an association between hydroxyzine and acute generalized exanthematous pustulosis (AGEP), based on findings in FAERS and the medical literature, which included information on a temporal relationship, positive dechallenges, and positive rechallenges. 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 products as follows:

PRECAUTIONS (add at the end of the section)
Acute Generalized Exanthematous Pustulosis (AGEP)
Hydroxyzine may rarely cause acute generalized exanthematous pustulosis (AGEP), a serious skin reaction characterized by fever and numerous small, superficial, non-follicular, sterile pustules, arising within large areas of edematous erythema. Inform

patients about the signs of AGEP, and discontinue hydroxyzine at the first appearance of a skin rash, worsening of pre-existing skin reactions which hydroxyzine may be used to treat, or any other sign of hypersensitivity. If signs or symptoms suggest AGEP, use of hydroxyzine should not be resumed and alternative therapy should be considered. Avoid cetirizine or levocetirizine in patients who have experienced AGEP or other hypersensitivity reactions with hydroxyzine, due to the risk of cross-sensitivity.

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). Your supplement should only include proposed changes made in accordance with the above direction. Any other proposed labeling changes should be submitted in a separate supplement and should not be identified as a safety labeling change.

We have determined that an extension of the discussion period will be warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for your supplement or rebuttal statement will begin when the submission is received, and will end within 90 days from the date of this letter, unless additional discussion extensions are warranted.

Failure to submit a response within 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A), misbranding charges under section 502(z), and an order under 505(o)(4) 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, contact Kyle Snyder, Labeling Project Manager, at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

Sincerely,

{see appended signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
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/

CAROL A HOLQUIST
08/11/2016