



ANDAs 040600 (10 mg), 040602 (25 mg), and 040604 (50 mg)

**LABELING ORDER**

Mikah Pharma LLC  
20 Kilmar Drive  
Hillsborough, NJ 08844

Attention: Nasrat Hakim  
President

Dear Mr. Hakim:

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 Tablets USP, 10 mg, 25 mg, and 50 mg.

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 tablets to address the risk of an association between the use of hydroxyzine hydrochloride tablets and fixed drug eruptions, cross-sensitivity between hydroxyzine hydrochloride tablet and cetirizine hydrochloride, and between cetirizine hydrochloride and levocetirizine hydrochloride and cross-sensitivity on positive lesional patch testing between hydroxyzine hydrochloride tablet and levocetirizine hydrochloride. 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

The 30 days have passed and we have not received any submission from you addressing our letter dated April 9, 2014.

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), changes being effected (CBE) supplements 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 submissions 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

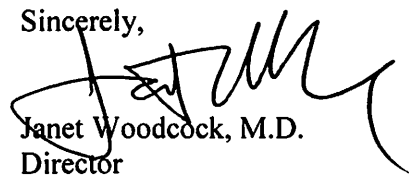
Refer to the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level" for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Amy Bertha, CDER Formal Dispute Resolution Project Manager, 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.

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,

A handwritten signature in black ink, appearing to read 'Janet Woodcock', written over the printed name.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

**ENCLOSURE(S): Safety Labeling Change Notification Letter**



ANDAs 040600 (10 mg), 040602 (25 mg), and 040604 (50 mg)

## SAFETY LABELING CHANGE NOTIFICATION

Mikah Pharma LLC  
Attention: Nasrat Hakim  
20 Kilmar Drive  
Hillsborough, NJ 08844

Dear Sir/Madam:

Please refer to your Abbreviated New Drug Applications (ANDAs) submitted under section 505(b) 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 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 Tablets, USP was approved on December 28, 2004, we have become aware of postmarketing reports in the FDA Adverse Event Reporting System (FAERS) that suggest an association between the use of Hydroxyzine Hydrochloride Tablets, USP and fixed drug eruptions. We have also become aware of published case reports of cross-sensitivity between Hydroxyzine Hydrochloride Tablets, USP and cetirizine hydrochloride, and between cetirizine hydrochloride and levocetirizine hydrochloride. Cross-sensitivity on positive lesional patch testing is also described between Hydroxyzine Hydrochloride Tablets, USP and levocetirizine hydrochloride. 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 Tablets, USP as follows:

Revise the **CONTRAINDICATIONS** section of the package insert to add the following statement before the existing information.

### CONTRAINDICATIONS

Oral hydroxyzine hydrochloride is contraindicated in patients with known hypersensitivity to hydroxyzine hydrochloride products, and in patients with known hypersensitivity to cetirizine hydrochloride or levocetirizine hydrochloride.

Revise the **ADVERSE REACTIONS** section of the package insert to add the following statement before the existing information.

## **ADVERSE REACTIONS**

### **Skin and Appendages:**

Oral hydroxyzine hydrochloride is associated with fixed drug eruptions in postmarketing reports.

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ROBERT L WEST

04/09/2014

Deputy Director, Office of Generic Drugs, for  
Kathleen Uhl, M.D.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CARRIE L LEMLEY  
06/03/2014