DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 040688

**LABELING ORDER**

WraSer Pharmaceuticals
Attention: Heath Wray
121 Marketridge Road
Ridgeland, MS 39157

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules, 356.4 mg/30 mg/16 mg.

On February 19, 2013, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related changes to the labeling of Acetaminophen and Codeine Phosphate Tablets, USP to address the risk of children developing serious adverse effects or dying after taking codeine for pain relief after tonsillectomy and/or adenoidectomy for obstructive sleep apnea. 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 prior approval 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 acknowledge receipt of your correspondence dated March 17, 2013. 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 February 19, 2013 letter (attached). We also refer to our letter dated March 29, 2013, informing you that we determined that a 30-day extension of the discussion period was warranted to allow us to complete our review and reach agreement on the content of the labeling.

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 February 19, 2013, letter must be received by FDA by May 24, 2013, for Acetaminophen and Codeine Phosphate 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 May 14, 2013, 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." The appeal should be submitted as 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 submissions 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
7520 Standish Place
Rockville, MD 20855

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 May 14, 2013, 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 Carrie Lemley, Labeling Project Manager, at (240) 276-8986.

Sincerely,

*{See appended electronic signature page}*

Keith Webber, Ph.D.
Acting Director
Office of Pharmaceutical Science
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

ANDA 040688

**SAFETY LABELING CHANGE NOTIFICATION**

WraSer Pharmaceuticals
Attention: Stephen Payne
121 Marketridge Road
Ridgeland, MS 39157

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules, 356.4 mg/30 mg/16 mg.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety related labeling changes based upon new safety information that becomes available after approval of the drug or biological product.

Since Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules was approved on April 3, 2007, we have become aware of reports of children who developed serious adverse effects or died after taking codeine for pain relief after tonsillectomy and/or adenoidectomy for obstructive sleep apnea. Recently, three pediatric deaths and one non-fatal but life-threatening case of respiratory depression were documented in the medical literature[1,2]. These children (ages two to five) had evidence of a genetic polymorphism of cytochrome P450 2D6 (CYP2D6), resulting in their ability to convert codeine into life-threatening or fatal amounts of morphine in the body. All children had received doses of codeine that were within the typical dose range. 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 codeine-containing products as follows:

- Addition of the following statement to the current boxed warning:

**WARNING: Death Related to Ultra-Rapid Metabolism of Codeine to Morphine**

[1] Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med 2009;361:827-8.

[2] Kelly LE, Rieder M, van den Anker J, Malkin B, Ross C, Neely MN, et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics 2012;129:e1343-7.

**Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.**

- Addition of a Contraindication that states, "Dihydrocodeine-containing products are contraindicated for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy." This contraindication should be listed first.
- Addition to the Warnings section of a subsection called "Death Related to Ultra-Rapid Metabolism of Codeine to Morphine".
    - This Warning should follow the "Hepatotoxicity" section and precede the "Hypersensitivity/Anaphylaxis" section

**Death Related to Ultra-Rapid Metabolism of Codeine to Morphine**

Respiratory depression and death have occurred in children who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine [see *Precautions, Nursing Mothers*].

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. These individuals convert dihydrocodeine into its active metabolite, dihydromorphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum dihydromorphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see *Overdosage*].

Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Dihydrocodeine-containing products are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy [*see Contraindications*].

When prescribing dihydrocodeine-containing products, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose [see O*verdosage*].

- Addition of these bullets to the list of "Information for Patients/Caregivers":

Advise patients that some people have a genetic variation that results in dihydrocodeine changing into dihydromorphine more rapidly and completely than other people. Most people are unaware of whether they are an ultra-rapid dihydrocodeine metabolizer or not. These higher-than-normal levels of dihydromorphine in the blood may lead to life-threatening or fatal respiratory depression

or signs of overdose such as extreme sleepiness, confusion, or shallow breathing. Children with this genetic variation who were prescribed codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea may be at greatest risk based on reports of several deaths in this population due to respiratory depression. Dihydrocodeine-containing products are contraindicated in all children who undergo tonsillectomy and/or adenoidectomy. Advise caregivers of children receiving dihydrocodeine-containing products for other reasons to monitor for signs of respiratory depression.

Advise patients that nursing mothers taking dihydrocodeine-containing products can have higher dihydromorphine levels in their breast milk if they are ultra-rapid metabolizers. These higher levels of dihydromorphine in breast milk may lead to life-threatening or fatal side effects in nursing babies. Advise nursing mothers to watch for signs of dihydromorphine toxicity in their infants which includes increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness. Instruct nursing mothers to talk to the baby's doctor immediately if they notice these signs and, if they cannot reach the doctor right away, to take the baby to an emergency room or call 911 (or local emergency services).

- Addition of the following statement to the "Nursing Mothers" subsection of Precautions

Dihydrocodeine bitartrate is secreted into human milk. In women with normal dihydrocodeine metabolism (normal CYP2D6 activity), the amount of dihydrocodeine secreted into human milk is low and dose-dependent. However, some women are ultra-rapid metabolizers of dihydrocodeine. These women achieve higher-than-expected serum levels of dihydrocodeine's active metabolite, dihydromorphine, leading to higher-than-expected levels of dihydromorphine in breast milk and potentially dangerously high serum dihydromorphine levels in their breastfed infants. Therefore, maternal use of dihydrocodeine can potentially lead to serious adverse reactions, including death, in nursing infants.

The risk of infant exposure to dihydrocodeine and dihydromorphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and the baby. Caution should be exercised when dihydrocodeine is administered to a nursing woman. If a dihydrocodeine containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Mothers using dihydrocodeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Nursing mothers who are ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of dihydrocodeine-containing products during breast-feeding *[see Warnings]*.

~~Dihydrocodeine bitartrate,~~ Acetaminophen and caffeine are also excreted in breast milk in small amounts~~., but the significance of their effects on nursing infants is not known.~~ Because of the potential for serious adverse reactions in nursing infants from this combination product, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

- Addition of the following statement to the "Pediatric Use" subsection in Precautions to highlight the risk of respiratory depression and death, particularly in children who are undergoing adenotonsillectomy.

> Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme CYP2D6 or high morphine concentrations). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Dihydrocodeine-containing products are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy [*see Contraindications*].

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement (PAS) proposing changes to the approved labeling in accordance with the above direction and pay the required PAS fee as required by the Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III), 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.

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 monetary 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) – 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 Carrie Lemley, Labeling Project Manager at (240) 276-8986.

Sincerely,

*{See appended electronic signature page}*

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

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ROBERT L WEST

02/19/2013

Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

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/s/

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KEITH O WEBBER
05/10/2013