DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDAs 074436 (10 mg)
073143 (10 mg)

LABELING ORDER

Watson Laboratories, Inc.
Attention: Joyce DelGaudio
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. DelGaudio:

Please refer to your Abbreviated New Drug Applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cyclobenzaprine Hydrochloride Tablets USP, 10 mg.

On February 7, 2013, 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 Cyclobenzaprine Hydrochloride to address the risk of serotonin syndrome with cyclobenzaprine in combination with other medications. 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 26, 2013. However, because you failed to respond to our February 7, 2013 letter within 30 days, you forfeited the discussion period. 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 7, 2013 letter (attached) and additional changes as modified below:

PACKAGE INSERT:

a. WARNINGS; *Seratonin Syndrome*; paragraph 1; sentence 1: Please revise to read: "The development of a potentially life-threatening serotonin syndrome has been reported with Cyclobenzaprine Hydrochloride when used in combination with other drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tramadol, bupropion, meperidine, verapamil, or (MAO) inhibitors."

b. PRECAUTIONS
   i) *Information for Patients*; paragraph 2: Please revise to read: "Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of Cyclobenzaprine Hydrochloride and other drugs, such as SSRIs, SNRIs, TCAs,

tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. Patients should be advised of the signs and symptoms of serotonin syndrome, and be instructed to seek medical care immediately if they experience these symptoms (see WARNINGS, and see PRECAUTIONS, Drug Interactions)."

ii) *Drug Interactions*; paragraph 1; sentence 2: Please revise to read: "Postmarketing cases of serotonin syndrome have been reported during combined use of Cyclobenzaprine Hydrochloride and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors."

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 7, 2013, letter, as modified in accordance with this letter, must be received by FDA by April 26, 2013, for Cyclobenzaprine Hydrochloride Tablets USP, 10 mg.

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 April 16, 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 April 16, 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

ENCLOSURES: Safety Labeling Change Notification Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDAs 071611 (5 mg, 7.5 mg and 10 mg)
074436 (10 mg)
073143 (10 mg)

SAFETY LABELING CHANGE NOTIFICATION

Watson Laboratories, Inc. - Florida
Attention: Janet Vaughn
4955 Orange Drive
Ft. Lauderdale, FL 33314

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 Cyclobenzaprine Hydrochloride Tablets USP, 5 mg, 7.5 mg and 10 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 Cyclobenzaprine Hydrochloride Tablets, USP were approved on February 29, 1988, November 27, 1991 and November 30, 1994, we have become aware of post-marketing reports of serotonin syndrome with cyclobenzaprine in combination with other medications (e.g. selective serotonin reuptake inhibitors). This safety issue is further supported by literature linking the pharmacology of cyclobenzaprine and serotonin syndrome (Mestres J et al. Clin Pharm Ther. 2011;90(5):662-665). 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 Cyclobenzaprine Hydrochloride products as follows:

In the **WARNINGS** section, at the beginning of the section, add the following:

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with Cyclobenzaprine Hydrochloride when used in combination with other drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tramadol, bupropion, meperidine, verapamil, or monoamine oxidase (MAO) inhibitors. The concomitant use of

> Cyclobenzaprine Hydrochloride with MAO inhibitors is contraindicated (see CONTRAINDICATIONS). Serotonin syndrome symptoms may include mental status changes (e.g., confusion, agitation, hallucinations), autonomic instability (e.g., diaphoresis, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., tremor, ataxia, hyperreflexia, clonus, muscle rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Treatment with Cyclobenzaprine Hydrochloride and any concomitant serotonergic agents should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated. If concomitant treatment with Cyclobenzaprine Hydrochloride and other serotonergic drugs is clinically warranted, careful observation is advised, particularly during treatment initiation or dose increases (see PRECAUTIONS, Drug Interactions).

In the **PRECAUTIONS** section, in the **Information for Patients** subsection, add the following as the second paragraph after the currently approved text:

> Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of Cyclobenzaprine Hydrochloride and other drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tramadol, bupropion, meperidine, verapamil, or monoamine oxidase (MAO) inhibitors. Patients should be advised of the signs and symptoms of serotonin syndrome, and be instructed to seek medical care immediately if they experience these symptoms (see WARNINGS, and see PRECAUTIONS, Drug Interactions).

In the **PRECAUTIONS** section, in the **Drug Interactions** subsection, revise the first paragraph to read as follows:

> Cyclobenzaprine may have life threatening interactions with MAO inhibitors (see CONTRAINDICATIONS). Postmarketing cases of serotonin syndrome have been reported during combined use of Cyclobenzaprine Hydrochloride and other drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tramadol, bupropion, meperidine, verapamil, or monoamine oxidase (MAO) inhibitors. If concomitant treatment with Cyclobenzaprine Hydrochloride and other serotonergic drugs is clinically warranted, careful observation is advised, particularly during treatment initiation or dose increases (see WARNINGS).

In the **ADVERSE REACTIONS** section, in the section regarding post-marketing experience, add serotonin syndrome to the end of the list of adverse reactions in the *Nervous System and Psychiatric* subsection. The text should read as follows.

> *Nervous System and Psychiatric:* Seizures, ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis, abnormal thinking and dreaming; hallucinations; excitement; paresthesia; diplopia, serotonin syndrome.

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 applications have 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) – REBUTTAL (CHANGE NOT WARRANTED)."

Prominently identify subsequent submissions related to the safety labeling changes supplements 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

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

02/07/2013

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

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

/s/

KEITH O WEBBER
04/11/2013