U.S. FOOD & DRUG ADMINISTRATION

ANDAs 070765
070766

LABELING ORDER

ANDA Repository, LLC
3477 Corporate Parkway; Suite 100
Center Valley, PA 18034
Attention: Tanya Dobash
President

Dear Tanya Dobash:

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

On March 14, 2025, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety labeling changes to the labeling of amitriptyline products to address the serious risk of hyponatremia. 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 March 14, 2025.

You failed to respond to our March 14, 2025, notification letter within 30 days. 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 March 14, 2025, 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 March 14, 2025, letter must be received by FDA by July 9, 2025, for Chlordiazepoxide and Amitriptyline 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:

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

Alternatively, by June 29, 2025, 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*[1]. 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:

Melissa Sage
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Building 51, Room 6158
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:

Carol Yun
Labeling Project Manager
Office of Generic Drugs
Food and Drug Administration
Bldg. 75, Room 3631
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 Melissa Sage, CDER Formal Dispute Resolution Project Manager, at (301) 796-6449. Appeals received by the Agency later than June 29, 2025, 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 Carol Yun, Labeling Project Manager, at (240) 402 - 6244 or carol.yun@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Iilun Murphy, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Safety Labeling Change Notification Letter

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

ANDAs 070765 and 070766

SAFETY LABELING CHANGE NOTIFICATION

ANDA Repository, LLC
3477 Corporate Parkway, Suite 100
Center Valley, PA 18034
Attention: Tanya Dobash
President

Dear Tanya Dobash:

This notification is regarding your Abbreviated New Drug Applications (ANDAs) for Chlordiazepoxide and Amitriptyline Hydrochloride Tablets, USP.

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product.

Since Chlordiazepoxide and Amitriptyline Hydrochloride Tablets, USP, were originally approved, we have become aware of an association between syndrome of inappropriate antidiuretic hormone secretion (SIADH) and chlordiazepoxide and amitriptyline use. This information is derived from post marketing cases from the FDA Adverse Event Reporting System and medical literature. We have determined that amitriptyline is included in a class of products that have the potential for the same serious risk of hyponatremia. 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 all amitriptyline products as follows:

(Under WARNINGS, add the following before “Angle-Closure Glaucoma”):

WARNINGS

[…]

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Hyponatremia - Hyponatremia has occurred as a result of treatment with [ESTABLISHED NAME]. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included syncope, seizure, coma, respiratory arrest, and death.

In patients with symptomatic hyponatremia, discontinue [ESTABLISHED NAME] and institute appropriate medical intervention. Elderly patients, patients taking diuretics, and those who are volume-depleted may be at greater risk of developing hyponatremia with [ESTABLISHED NAME].

Angle-Closure Glaucoma: The pupillary dilation…

[…]

ADVERSE REACTIONS

(Add "hyponatremia" at the end of "Other" subsection):

Other: … hyponatremia.

MEDICATION GUIDE:

*(Under "**Before you take [ESTABLISHED NAME], tell your healthcare provider**…", add the following bullet as follows"):*

[…]

- plan to have surgery
- have low sodium levels in your blood
- receive electroconvulsive therapy (ECT)

[…]

*(Under "**What are the possible side effects of…**", add the following, after "**Abuse and dependence**"):*

Low sodium levels in your blood (hyponatremia). Low sodium levels in your blood that may be serious and may cause death, can happen during treatment with [ESTABLISHED NAME]. Elderly

people and people who take certain medicines may be at a greater risk for developing low sodium levels in your blood. Signs and symptoms may include:

- headache
- difficulty concentrating
- memory changes
- confusion
- weakness and unsteadiness on your feet which can lead to falls

In more severe or more sudden cases, signs and symptoms include:

- seeing or hearing things that are not real (hallucinations)
- fainting
- seizures
- coma
- stopping breathing (respiratory arrest)

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[1]. 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 by June 9, 2025, unless additional discussion extensions are warranted.

[1] If you submit a CBE-0 supplement and FDA determines that modifications to the proposed language above are warranted based on FDA's review of another application holder's PAS or a discussion period in accordance with section 505(o)(4), you will need to make conforming labeling revisions in an amendment to your CBE-0 supplement.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Requirements under section 505(o)(4) apply to applications for prescription drugs under section 505(b) of the FD&C Act, applications under section 262 of title 42, and applications under section 505(j) of the FD&C Act without a currently marketed reference listed drug approved under section 505(c), 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*.

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

In addition, we recommend other revisions that are not based on new safety information as defined in section 505-1(b)(3) of the FDCA. These changes include the addition of serotonin syndrome under the Warnings section and to the Medication Guide. We recommend that you include the following revisions in the supplement described above.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

REQUESTED CHANGES TO LABELING

(Add the following before "Activation of Mania or Hypomania"):

WARNINGS

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome has been reported with tricyclic antidepressants, including [ESTABLISHED NAME], alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, SSRI/SNRI, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of [ESTABLISHED NAME] with MAOIs intended to treat psychiatric disorders is contraindicated. [ESTABLISHED NAME] should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking [ESTABLISHED NAME]. [ESTABLISHED NAME] should be discontinued before initiating treatment with the MAOI (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION). If concomitant use of [ESTABLISHED NAME] with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases. Treatment with [ESTABLISHED NAME] and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

*(Add the following after "**Call a healthcare provider right away if you**…" as a new section):*

MEDICATION GUIDE

- **Serotonin Syndrome.** This condition can be life-threatening and symptoms may include:
  - agitation, hallucinations, coma, or other changes in mental status
  - racing heartbeat, high or low blood pressure
  - coordination problems or muscle twitching (overactive reflexes)
  - nausea, vomiting, or diarrhea
  - sweating or fever
  - muscle rigidity

If you have any questions, contact Sunny Pyon, Labeling Project Manager, at (240) 402-9293 or sunny.pyon@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARAH G KURTZ
03/14/2025 12:37:52 PM

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

IILUN C MURPHY
06/24/2025 08:59:11 AM