

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-246

OTHER ACTION LETTER(s)



NDA 22-246

COMPLETE RESPONSE

Wilmington Pharmaceuticals
Attention: Eugene Haley
Chief Executive Officer
1213 Culbreth Drive, Suite 230
Wilmington, NC 28405

Dear Mr. Haley:

Please refer to your new drug application (NDA) dated November 5, 2007, which was withdrawn January 3, 2008, and your January 29, 2008, NDA resubmission received January 30, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Metozolv ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets, 5 mg and 10 mg for the relief of symptomatic gastroesophageal reflux and for the relief of symptoms associated with diabetic gastroparesis (diabetic gastric stasis).

We acknowledge receipt of your amendments dated April 8, April 21, May 20, June 9, June 27, June 30, July 16, July 31, August 26, September 8, September 11, September 18, October 8, October 22, December 5, December 10, 2008, and January 26, 2009.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. Before this application may be approved, you must submit a proposed REMS and labeling as described below:

1. RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to provide FDA with new authorities to require submission of a Risk Evaluation and Mitigation Strategy (REMS) if the FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

Current labeling for approved metoclopramide products warns of the risk of tardive dyskinesia, a serious movement disorder, with chronic metoclopramide treatment. Tardive dyskinesia is often irreversible. Several risk factors, including female gender, advanced age, treatment duration and total cumulative dose have been described. Recently published analyses suggest that metoclopramide has surpassed haloperidol as the most common cause of drug-induced movement disorders.^{1,2} A published FDA analysis of metoclopramide utilization patterns showed that

¹ Kenney C, Hunter C, Davidson A, Jankovic J. Metoclopramide, an increasingly recognized cause of tardive dyskinesia. *J Clin Pharmacol* 2008; 48:379-384.

prescription claims for cumulative periods longer than 90 days were recorded for a substantial portion of patients in that study.³ In addition, we have become aware of continued spontaneous reports to the FDA of tardive dyskinesia associated with metoclopramide use. Exposure greater than 12 weeks was evident in a majority of these reports.

Therefore, in accordance with section 505-1 of the FDCA, we have determined that a REMS for Metozolv ODT is necessary to ensure that the benefits of the drug outweigh the risks of tardive dyskinesia. The REMS, once approved, will create enforceable obligations.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Metozolv ODT poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Metozolv ODT. FDA has determined that Metozolv ODT is a product for which patient labeling could help prevent serious adverse events and that Metozolv ODT is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Metozolv ODT. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Metozolv ODT.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Metozolv ODT. Additionally, all relevant proposed REMS materials should be appended to the proposed REMS. Once FDA finds the content acceptable, we will include these documents as an attachment to the approval letter that includes the REMS.

² Pasricha PJ, Pehlivanov N, Sugumar A, and Jankovic J. Drug Insight: from disturbed motility to disordered movement – a review of the clinical benefits and medicolegal risks of metoclopramide. *Nat Clin Pract Gastroenterol Hepatol* 2006 Mar; 3(3):138-48.

³ Kaplan S, Staffa JA, Dal Pan GJ. Duration of therapy with metoclopramide: a prescription claims data study. *Pharmacoepi Drug Saf* 2007; 16: 878-881.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Information needed for the assessments should include but may not be limited to:

- a. Patients' understanding of the serious risks of Metozolv ODT
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

If you do not submit electronically, please send 5 copies of your proposed REMS and prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission.

NDA 22-246 PROPOSED REMS

On the first page of subsequent submissions related to the proposed REMS, prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-246 PROPOSED REMS-AMENDMENT

2. CHANGES TO YOUR DRAFT LABELING

Submit draft labeling that incorporates the Division's revisions below (additions are noted by underline and deletions are noted by ~~striketrough~~). In addition, submit updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

- The addition of a **Boxed Warning** to alert physicians of the risk of tardive dyskinesia with chronic use of metoclopramide, to include the following language:

(b) (4)



- Revisions to the **Warnings** section of the label to include the following language as the first subsection:



- Please submit draft **carton and container labeling** revised as follows:

Blister Label and Carton Labeling

1. Revise the presentation of the proprietary name so that the entire proprietary name is presented on the same line, with the same font size, color, and weight.
2. Spell out the complete dosage form “Orally Disintegrating Tablets” on the blister labels. Revise so that the complete dosage form immediately follows the established name, for example:

Metozolv ODT
(metoclopramide hydrochloride) Orally Disintegrating Tablets
XX mg*
*contains yy mg metoclopramide hydrochloride equivalent to xx mg metoclopramide.

Carton Labeling

1. Remove the graphic in the second “o” to improve the readability of the proprietary name and minimize confusion that the name is read as two names (Metozolv ODT).
2. Revise the presentation of the established name so that it has commensurate prominence to the proprietary name “taking into account all pertinent factors, including typography, layout, contrast, and other printing features” in accordance with 21 CFR 201.10 (g)(2).
3. Increase the prominence of the strength commensurate with the size of the proprietary name. Additionally, differentiate the product strengths by boxing, highlighting, using a different color font, or some other means.
4. Consider using a different color schema for one of the strengths (not just red and blue) to better distinguish between the two strengths.
5. Relocate the NDC number to appear in accordance with 21 CFR 207.35(b)(3)(i).
6. Add the following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide**".

3. ADDITIONAL DEFICIENCY:

The stability commitment should be revised to read as follows:

(b) (4)

FACILITY INSPECTIONS

We have completed inspection of your drug product and drug substance manufacturing facility and found to be acceptable.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: REMS Template

Appendix A- REMS Template

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

- A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;
- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B), (C), and (D), listed above.

E. Timetable for Submission of Assessments

Specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks.

Appendix B - REMS Supporting Document Template

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
 - a. Additional Potential Elements
 - i. Medication Guide
 - ii. Patient Package Insert
 - iii. Communication Plan
 - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
 - c. Implementation System
 - d. Timetable for Assessment of the REMS
4. Information Needed for Assessments
5. Other Relevant Information

**This is a representation of an electronic record that was signed electronically and
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/s/

Joyce Korvick
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