

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-246

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

NDA 22-246
METOZOLV™ ODT
(metoclopramide hydrochloride) Orally Disintegrating Tablets
5 mg & 10 mg

Salix Pharmaceuticals, Inc.
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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S)

The goal of this REMS is to minimize the risk of tardive dyskensia associated with the long-term use for METOZOLV™ ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets.

II. REMS ELEMENTS

A. Medication Guide

All professional samples given to patients by a health care professional shall include a Medication Guide enclosed in the carton to ensure that the safety information is distributed to the patient. The sample carton will prominently state: "Dispense the enclosed Medication Guide to each patient." Because there is only one blister sleeve per sample carton, the sleeve does not require a dispensing statement.

Each trade carton will contain four (4) medication guides with each box of 100 orally disintegrating tablets (10 blister sleeves). The number of Medication Guides is based upon research that indicates that the average number of tablets per prescription is currently 97 tablets. This will ensure that there is a sufficient number of medication guides provided with the product such that a dispenser can provide a medication guide with each prescription filled / refilled. In compliance with 21 CFR 208.24, the trade carton will prominently state: "Dispense the enclosed Medication Guide to each patient." Similarly, each blister sleeve in the trade carton will state: "Dispense the accompanying Medication Guide to each patient."

B. Communication Plan

This REMS for METOZOLV™ ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets does not require a Communication Plan.

C. Elements to Assure Safe Use

This REMS for METOZOLV™ ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets does not require Elements to Assure Safe Use.

D. Implementation System

This REMS for METOZOLV™ ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets does not require an Implementation System.

E. Timetable for Submission of Assessments

REMS Assessments will be submitted to FDA 18 months, 3 years, and 7 years after REMS approval.

The reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment.

REMS SUPPORTING DOCUMENT

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1. BACKGROUND

On February 26, 2009, the Food and Drug Administration (FDA) issued a Complete Response letter to Wilmington Pharmaceuticals (Wilmington) for its New Drug Application (NDA) 22-246. This letter stated that the application cannot be approved in its present form because under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), the FDA has determined that the risks associated long-term use of metoclopramide increases the risk of tardive dyskinesia. The Complete Response required, among other things, that Wilmington create a Medication Guide (Med Guide) to provide safety information to patients and a distribution plan for this Med Guide be outlined in a Risk Evaluation and Mitigation Strategy (REMS). This REMS sets forth the steps Wilmington will undertake to ensure that patients are informed of the possibility of tardive dyskinesia when using Metozolv ODT long-term and the proper administration of the tablets to prevent any such occurrence.

Wilmington provided a REMS, Medication Guide and REMS Supporting Document to the FDA on March 10, 2009. A fax was received by Wilmington on July 7, 2009 containing comments and information requests from the FDA. The REMS Supporting Document has been revised appropriately to correspond with the revised REMS.

2. GOALS

The goal of this REMS is to minimize the risk of tardive dyskensia associated with the long-term use for METOZOLV™ ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets.

3. SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

a. Additional Potential Elements

i. Medication Guide

Each trade carton will contain four (4) medication guides with each box of 100 orally disintegrating tablets (10 blister sleeves). The number of Medication Guides is based upon research that indicates that the average number of tablets per prescription is currently 97 tablets. This will ensure that there is a sufficient number of medication guides provided with the product such that a dispenser can provide a medication guide with each prescription filled / refilled. In compliance with 21 CFR 208.24, the trade carton will prominently state: "Dispense the enclosed Medication Guide to each patient." Similarly, each blister sleeve in the trade carton will state: "Dispense the accompanying Medication Guide to each patient."

All professional samples given to patients by a health care professional shall include a Medication Guide enclosed in the sample carton to ensure that the safety information is distributed to the patient. The sample carton will prominently state: "Dispense the enclosed Medication Guide to each patient." Because there is only one blister sleeve per sample carton, the sleeve does not require a dispensing statement.

ii. Communication Plan

This REMS for METOZOLV™ ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets does not require a Communication Plan.

b. Elements to Assure Safe Use

This REMS for METOZOLV™ ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets does not require Elements to Assure Safe Use.

c. Implementation System

This REMS for METOZOLV™ ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets does not require an Implementation System.

d. Timetable for Assessment of the REMS

REMS Assessments will be submitted to FDA 18 months, 3 years, and 7 years after REMS approval.

The reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment to facilitate inclusion of as much information as possible while allowing a reasonable time to prepare the assessment.

4. INFORMATION NEEDED FOR ASSESSMENTS

The assessment will include an evaluation of:

- 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
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

A geographically based group of health care professionals will be contracted to hand out a survey to Metozolv ODT patients at the time of script writing during the assessment period. The patient will be prompted to complete the survey after Metozolv ODT has been dispensed. The survey will include questions regarding the patient's comprehension of the potential risks associated with and safety information about Metozolv ODT as described in the Medication Guide. The survey will also ask patients if they received a

Medication Guide from the pharmacist to assess the distribution and dispensing of the Med Guide. If the patient responds that a Med Guide was not dispensed with Metozolv ODT, the name and location of the pharmacy, as requested on the survey, will be noted. Corrective actions will be determined dependent on the reason for failure.

5. OTHER RELEVANT INFORMATION

None.

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation III
Division of Gastroenterology Products**

NDA #: 17-854
Product: Reglan (metoclopramide tablets, USP) Tablets
SPONSOR: Alaven Pharmaceutical LLC.

NDA #: 21-793
Product: Reglan ODT (metoclopramide) Orally Disintegrating Tablets
SPONSOR: Alaven Pharmaceutical LLC.

ANDA#: 74-703
Product: Metoclopramide Oral Solution
SPONSOR: Morton Grove Pharmaceuticals, Inc.

ANDA#: 71-402
Product: Metoclopramide Oral Solution
SPONSOR: ANI Pharmaceuticals, Inc.

ANDA#: 72-744
Product: Metoclopramide Oral Solution
SPONSOR: Pharmaceutical Associates, Inc.

ANDA#: 73-680
Product: Metoclopramide Oral Solution
SPONSOR: Silarx Pharmaceuticals, Inc.

NDA #: 22-246
Products: Metozolv ODT (metoclopramide) Orally Disintegrating Tablets
SPONSOR: Wilmington Pharmaceuticals

FROM: Joyce Korvick, MD MPH
Deputy Director of Safety

DATE: February 26, 2009

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 authorize FDA to require the submission of a REMS for an approved drug if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

Reglan Tablets and Reglan ODT Orally Disintegrating Tablets were approved on December 30, 1980 and June 10, 2005, respectively. The Metoclopramide Oral Solution products were approved on May 28, 1991 (ANDA 72-744), October 27, 1992 (ANDA 73-680), June 25, 1993 (ANDA 71-402), and October 31, 1997 (ANDA 74-703). The NDA for Metozolv ODT, received January 29, 2008, is currently under review. Current product 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 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. This information was not available when Reglan Tablets, Reglan ODT Orally Disintegrating Tablets, and the four Metoclopramide oral solution products referenced above were granted marketing authorization. We consider this information to be “new safety information” as defined in FDAAA.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of metoclopramide outweigh its risks. In reaching this determination we considered the following:

- A. Drug utilization data indicate that metoclopramide is used in about (b) (4) patients in the US and the number of patients using the product has been rising. In addition, most of the uses from the years 2002 to 2007 were for gastroesophageal reflux disease (GERD).⁴ Although a relatively small proportion of metoclopramide use was for gastroparesis, metoclopramide dominated the market share for use in this condition.
- B. Metoclopramide is approved for the treatment of patients with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy, and

⁴ For the purpose of this memo, patients with the labeled indication “gastroesophageal reflux who fail to respond to conventional therapy” are considered to have “gastroesophageal reflux disease” or GERD.

for diabetic gastroparesis (diabetic gastric stasis). The treatment of these patients includes the healing of esophageal ulcers and erosions in addition to symptomatic treatment. Ulcers and erosions can progress to perforations of the esophagus, serious bleeding and potentially cancer of the esophagus. Diabetic gastric stasis is a serious condition that can lead to weight loss due to the inability to ingest an adequate amount of food, malabsorption, and malnutrition. This is a serious issue especially in fragile diabetics making it difficult to control the patient's blood sugar.

- C. Patients with symptomatic gastroesophageal reflux will experience fewer symptoms and, in addition, those with esophageal erosions that are healed may not experience serious bleeding and perforation. Short-term treatment has not been shown to prevent esophageal cancer.

Patients with diabetic gastroparesis who respond to this therapy will have the ability to eat and retain a normal diet volume. In addition, symptoms such as nausea, vomiting, abdominal pain and bloating will improve. These improvements may lead to better nutrition and better blood sugar control.

- D. Symptomatic Gastroesophageal Reflux: Metoclopramide is approved for short-term (4-12 weeks) treatment in adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy. In addition, for patients with gastroesophageal erosions, 12 weeks of therapy has been successful. Therapy longer than 12 weeks has not been evaluated and is not recommended.

Diabetic Gastroparesis: Metoclopramide is approved for the relief of symptoms associated with diabetic gastroparesis. Product labeling recommends treatment for "two to eight weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation". It further states that since diabetic gastric stasis is frequently recurrent, metoclopramide "should be reinstated at the earliest manifestation." This implies that metoclopramide may be used episodically in these patients.

- E. Chronic treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with the duration of treatment and the total cumulative dose. The elderly, especially elderly women, are most likely to develop this condition.

Metoclopramide therapy should routinely be discontinued in patients who develop signs or symptoms of tardive dyskinesia. There is no known treatment for tardive dyskinesia; however, in some patients symptoms may lessen or resolve after metoclopramide treatment is stopped.

Prolonged treatment (greater than 12 weeks) with metoclopramide should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risks to the patient of developing tardive dyskinesia.

- F. The drug metoclopramide, found in Reglan Tablets, Reglan ODT Orally Disintegrating Tablets, and the four Metoclopramide Oral Solution products referenced above, and the pending application for Metozolv ODT, is not an NME.

In accordance with section 505-1 of the FDCA, 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 metoclopramide 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 metoclopramide. FDA has determined that metoclopramide is a product that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use metoclopramide. FDA has also determined that metoclopramide is a product for which patient labeling could help prevent serious adverse events.

The elements of the REMS for Reglan Tablets, Reglan ODT Orally Disintegrating Tablets, and Metozolv ODT will be a Medication Guide and a timetable for submission of assessments of the REMS. The elements of the REMS for the four Metoclopramide Oral Solution products referenced above will be a Medication Guide only. To protect the public health, FDA is requiring all sponsors of approved metoclopramide products to submit a proposed REMS within 30 days of receipt of FDA's notification that a REMS for metoclopramide is required. Wilmington Pharmaceuticals, the sponsor of the pending NDA for Metozolv ODT, will need to submit a proposed REMS to its application before evaluation of the NDA can continue.

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

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.

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/s/

Joyce Korvick
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MEDICAL OFFICER