

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-246**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**DATE:** 2/20/2009

**FROM:** Ruyi He, M.D.  
Medical Team Leader  
Division of Gastroenterology Products/ODE III

**TO:** Donna Griebel, M.D.  
Director  
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And

Joyce Korvick, M.D., M.P.H.  
Deputy Director for Safety  
Division of Gastroenterology Products/ODE III

**SUBJECT:** GI Team Leader CR Comments  
NDA 22-246 Metozolv ODT (metoclopramide) Orally Disintegrating  
Tablet

**THERAPEUTIC CLASS:** Prokinetic Agent

**APPLICANT:** Wilmington Pharmaceuticals

**FORMULATION:** Orally Disintegrating Tablets

**PROPOSED INDICATION:**

- For short-term (4-12 weeks) treatment in adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy.
- For the relief of symptoms associated with diabetic gastroparesis.

**RECOMMENDATION:**

I concur with Dr. Fathia Gibril's safety assessment and conclusion for NDA 22-246 Metozolv ODT (metoclopramide) that safety related changes should be included in the labeling and a Risk Evaluation and Mitigation Strategies (REMS) including Medication Guide is necessary to ensure that the benefits of the drug outweigh the risks. I recommend that complete response action be taken for NDA 22-246 at this review cycle. In order to get approval, the sponsor needs to provide following:

- 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 Tardive dyskinesia safety information as the first subsection.
- The addition of a **Medication Guide** that must include information about the serious risk of tardive dyskinesia and that will be considered part of the proposed REMS.

## **BACKGROUND:**

Metoclopramide is a prokinetic agent that has a complex mechanism of action. It enhances gastrointestinal motility. Anti-emetic effects of metoclopramide are mainly the result of central dopamine antagonism and increased gastric motility; it also possesses a weak 5-HT<sub>3</sub> receptor antagonism.

The Agency approved Reglan injectable formulation in 1979 (NDA 17-862), and Reglan tablets in 1980 (NDA 17-854). Reglan oral solution was approved in 1983, but subsequently was discontinued. In June 2005, orally disintegrating tablet (Reglan™ ODT) was approved (NDA 21-793) based on a single comparative bioequivalence study with the referenced listed drug (RLD) Regal tablet, but has not been marketed.

The oral formulations are indicated for the short-term (4-12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux diseases (GERD) who fail to respond to conventional therapy and for the relief of symptoms associated with acute and recurrent diabetic gastroparesis (2-8 weeks). The injectable formulation is indicated for the prevention of post-operative and cancer chemotherapy induced nausea/vomiting, for the relief of symptoms associated with acute and recurrent diabetic gastroparesis, to facilitate small bowel intubation, and as a diagnostic aid during gastrointestinal radiography.

The sponsor plans to cross-reference the efficacy and safety data contained in NDA 17-854 in support of a 505(b)(2) application for the new dosage form. It was agreed upon that if the pharmacokinetic (PK) profiles for the two formulations (i.e., 10 mg Reglan Tablet and the 10 mg orally disintegrating tablet) are the same, the preclinical studies for the original NDA may be sufficient to support the new formulation and the original clinical studies could support the new formulation.

In the current 505(b)(2) submission, the sponsor is seeking approval of a new metoclopramide orally disintegrating tablet (Metozolv ODT) 5 and 10 mg. The proposed indications and dosing regimen are the same as the reference listed drug (RLD) Reglan® tablet 5 and 10 mg. In support of the application (NDA 22-246) the sponsor submitted results from two comparative bioequivalence (BE) studies and from one relative bioavailability (food-effect) study in healthy volunteers.

## **DISCIPLINE REVIEW SUMMARY AND COMMENTARY:**

### **Efficacy**

No efficacy studies were submitted with this NDA.

Study 10643701 was a randomized, two-way crossover study under fasting conditions comparing the bioequivalence (BE) of a single dose of 10 mg Metozolv ODT to 10 mg Reglan tablet (RLD) in 44 healthy adults.

Study NA464 was a pilot BE study in 12 healthy adult volunteers to compare a single dose prototypic formulation of Metozolv ODT 10 mg vs. Reglan tablet 10 mg in fasted subjects. This was open-label, two-way crossover, randomized, single center study. This study was performed with a formulation different from a to-be-marketed formulation.

Study 10743701 was a single-dose, randomized, three-period crossover study that compared the bioavailability (BA) of a single fed and fasted dose of 10 mg Metozolv ODT as well as a single fed dose of 10 mg Reglan tablets (RLD). A total of 30 healthy adult subjects were enrolled.

For detail evaluation of above listed trials, please see FDA clinical pharmacology review.

### **Safety**

A total of 96 subjects were exposed to Metozolv ODT and 72 subjects were exposed to Reglan Tablets. The adverse experience profile seen with Metozolv ODT was similar to that of Reglan Tablets. Thirty-three (33) adverse events were reported after receiving Metozolv ODT and 30 adverse events were reported after receiving Reglan Tablets. All of the events experienced by the subjects were considered mild. There were no serious adverse events or death reported in these clinical trials.

The most frequently reported adverse events (greater than 4% occurrence) associated with Metozolv ODT were: nausea (4/96), and headache (5/96). The most frequently reported adverse events (greater than 4% occurrence) associated with Reglan Tablets were: nausea (4/72), abnormal blood count (3/72), increased blood pressure (3/72), decreased blood pressure (3/72), headache (3/72), and dizziness (3/72). The combined data from the fasted BE study and the food-effect study did not demonstrate any differences in the adverse event profile for Metozolv ODT compared to Reglan Tablets. For detail safety evaluation, please see Dr Fathia Gibril's review.

### **CMC**

Based on Dr. Gene Holbert's evaluation, this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product except for the post approval stability commitment. All facilities involved are in compliance with cGMP. For detail CMC evaluation, please see Dr. Gene Holbert's review dated January 30, 2009.

**Animal Pharmacology/Toxicology**

No new animal toxicology studies were submitted in this NDA. Based on Dr. Tamal K. Chakraborti's evaluation, this NDA is recommended for approval for the proposed use. Please see Dr. Tamal K. Chakraborti's review dated September 25, 2008 for details.

**Pharmacokinetics**

Based on Dr. Tapash Ghosh's evaluation, Wilmington Pharmaceuticals, LLC's METZOLV ODT 10 mg tablets (Test) are bioequivalent to REGLAN (metoclopramide) Tablets 10 mg (Reference by Schwarz Pharma, Inc.) under fasted conditions (Study 10643701). Comparison between METZOLV ODT (Test) and the reference Reglan tablet (Reference) demonstrated that the overall bioavailability (LnAUC<sub>0-t</sub> and LnAUC<sub>0-inf</sub>) of METZOLV ODT 10 mg tablet compared to REGLAN (metoclopramide) USP 10 mg Tablets (Schwarz Pharma, Inc.), was equivalent when both were taken in the fed state in terms of AUC. However, C<sub>max</sub> was approximately 24% lower for the test product compared to the reference product when both were taken following a high fat meal. Dr. Tapash Ghosh concluded that the information for the 10 mg strength is acceptable from OCP/DPE III perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the proposed package insert. For detail information, please see Dr. Tapash Ghosh's review dated November 3, 2008.

**Pharmacodynamics**

Other than the BA and BE studies (bridging studies of Metozolv ODT to Reglan tablets) Wilmington Pharmaceuticals did not conduct pharmacodynamic study.

**DISCUSSION/COMMENTS:**

The oral formulations of metoclopramide are indicated for the short-term (4-12 weeks) therapy for adults with symptomatic, documented GERD who fail to respond to conventional therapy and for the relief of symptoms associated with acute and recurrent diabetic gastroparesis (2-8 weeks). The duration of use not to exceed 12 weeks is reflected under Indications & Usage Section of the product label.

Metoclopramide is well known to cause movement disorders such as acute dystonic reaction, Parkinson-like symptoms and tardive dyskinesia (TD), which are reflected under WARNING section in the US package insert (USPI). In addition, the risk of developing irreversible movement disorders such as TD with prolonged use of metoclopramide has been a longstanding safety concern and has been described in the WARNING section of the Reglan tablets USPI as follow: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose. Less commonly,

the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible.

Despite the label recommendation that therapy should not to exceed 12 weeks, a prolonged use of the product has been reported according to the review dated June 27, 2008 by Dr Kate Gelperin (Epidemiologist), Division of Epidemiology, Office of Surveillance and Epidemiology (OSE). In US drug utilization data from 2002 to 2004 (b) (4) cumulative therapy with metoclopramide for longer than 90 days was observed for roughly 20% of patients.

In light of the serious risk of irreversible drug-induced movement disorders, metoclopramide use in chronic conditions such as GERD should be limited only to patients for whom other safer treatment options have been exhausted. Patients should be clearly instructed to be alert for early signs or symptoms of movement disorders, and to stop drug and contact their doctor immediately if any of these occur. I believe that heightened awareness of the risk of movement disorders with metoclopramide use is urgently needed.

I concur with Dr. Fathia Gibril and OSE recommendations that it is necessary to add a BOXED WARNING as a first step to call increased attention to the risk of movement disorders (TD), and Parkinson's disease which occur commonly during prolonged treatment with metoclopramide. The BOXED WARNING should include a clear statement that metoclopramide use, especially in chronic conditions such as GERD, should be restricted to patients who have exhausted other treatment options and metoclopramide should be discontinued if any signs or symptoms of movement disorder are noted by the patient or prescriber.

An appropriate risk communication plan, including Medication Guide is necessary to increase awareness of early signs of irreversible movement disorders (TD), and Parkinson's disease.

I agree with Dr. Fathia Gibril's comments that metoclopramide is the only product currently approved for diabetic gastroparesis indication. Although there are currently many approved medical therapies such as antisecretory agents (H<sub>2</sub>-receptor antagonists and proton pump inhibitors) available for GERD indication, the mechanism of action of metoclopramide is different from that of acid suppressing agents. Metoclopramide accelerates gastric emptying and has been shown to increase the resting tone of the lower esophageal sphincter pressure (LESP) in subjects with GERD and low LESP. As such, it would provide clinical benefits to a subpopulation who fail to respond to conventional therapies. Metoclopramide is approved as second line therapy for the indication (GERD).

In conclusion, I concur with Dr. Fathia Gibril's safety assessment and conclusion for NDA 22-246, Metozolv ODT (metoclopramide) that safety related changes should be included in the labeling and a Risk Evaluation and Mitigation Strategies (REMS) including Medication Guide is necessary to ensure that the benefits of the drug outweigh the risks. I recommend that complete response (CR) action be taken for

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MEDICAL OFFICER