

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-246

OTHER REVIEW(S)

MEMORANDUM

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

DATE: January 9, 2009

FROM: Samuel H. Chan, Pharm.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. *Marti K. Yan 1/9/2009*
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-246,
Metozolv (Zydis metoclopramide) ODT, 10mg
Sponsored by Wilmington Pharmaceuticals

TO: Dennis Bashaw, Pharm.D.,
Director, Division of Clinical Pharmacology 3,
OCP/OTS

At the request of OCP/OTS, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

Protocol 10647301:

"The Relative Bioavailability of Metoclopramide 10 mg Orally Disintegrating Tablets (Wilmington Pharmaceuticals) Compared to REGLAN® (metoclopramide) 10 mg Tablets (Schwarz Pharma) under Fasting Conditions"

The clinical portion of the above study was conducted at

(b) (4)

(b) (4) The analytical portion of the above study was conducted at

(b) (4)

(b) (4)

Following the audit of the clinical site at (b) (4) (1/7/09 - 1/8/09), Form FDA-483 was not issued. Following the audit of the analytical records at (b) (4) (12/15/08 - 12/18/08), Form FDA-483 was issued. Please note that DSI has not received (b) (4) response to the Form FDA-483 items as of 1/9/2009. The evaluation of the significant findings of the analytical study conduct follows:

- 1) **Failure to report all valid validation runs conducted for metoclopramide method 233.100.**
 - a) **The failed experiment of stock solution stability conducted on April 17, 2006 was excluded from the validation report without assignable cause.**
 - b) **The metabolite interference study of O-desmethyl metoclopramide was excluded from the validation report without assignable cause.**

Although it is objectionable that the firm failed to include all valid validation runs in the method validation reports, such deficiency did not have a significant impact on the validity of the study. For observation 1 (a), the firm conducted two additional stock solution stability studies for both Metoclopramide and the internal standard. The results of these two confirming stability studies were provided to FDA and the results were satisfactory. For observation 1 (b), the results of the study showed that there was no metabolite interference.

- 2) **Failure to document all aspects of study conduct. Specifically, there was no documentation to confirm that the autosampler injection sequence was verified.**

The firm claimed that the sample sequence was checked but not documented in writing.

- 3) **Failure to document and/or review thirty-two of fifty-two standard operating procedures (SOPs) annually per SOP 5.4.5. SOP 5.4.5 states that SOPs will be reviewed every year in the month of August and if no changes are needed a blanket statement stating the review date and action taken will be included in the SOP binder.**

Although it is objectionable that the firm failed to document the SOP revisions, the SOPs for analytical procedures were reviewed and were considered satisfactory.

Conclusions:

Following the above inspections, DSI recommends that the clinical and analytical portions of Study 10643701 be accepted for agency's review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.



Samuel H. Chan, Pharm.D.

Final Classifications:

VAI -
NAI -

(b) (4)

DSI/Vaccari
DSI GLPBB/chan/Rivera-Lopez/Patague/CF
HFR-SW1540/Martinez/Stone/BIMO
HFR-CE1515/Tammeriello/Rakestraw/BIMO
HFR-SW150/Glasgow/DIB
HFD-880/Bashaw/Dewey/Lee
Draft: SHC 1/7/09
Edit: MKY 1/7/09
DSI: (b) (4); O:\BE\EIRCOVER\22246wil.met
FACTS: (b) (4)

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Samuel Chan
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DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 21, 2009

To: Donna Griebel, M.D., Division Director
Division of Gastroenterology Products (DGP)

Through: Jodi Duckhorn, M.A., Team Leader
Division of Risk Management (DRISK)

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Reviewer
Division of Risk Management (DRISK)

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): METOZOLV ODT (metoclopramide hydrochloride) Orally
Disintegrating Tablets

Application
Type/Number: NDA 22-246

Applicant/sponsor: Wilmington Pharmaceuticals

OSE RCM #: 2009-604

1 INTRODUCTION

This review is written in response to a request from the Division of Gastroenterology Products (DGP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide for METOZOLV ODT (metoclopramide hydrochloride) orally disintegrating tablets).

FDA has determined that METOZOLV ODT (metoclopramide hydrochloride) orally disintegrating tablets 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 (metoclopramide hydrochloride) orally disintegrating tablets. FDA has determined that METOZOLV ODT (metoclopramide hydrochloride) orally disintegrating tablets is a product with a serious a significant public health concern that meets two of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: METOZOLV ODT (metoclopramide hydrochloride) orally disintegrating tablets 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' decision to use or continue to use; METOZOLV ODT (metoclopramide hydrochloride) orally disintegrating tablets is a product for which patient labeling could help prevent serious adverse events.

2 MATERIAL REVIEWED

- Draft METOZOLV ODT (metoclopramide hydrochloride) orally disintegrating tablets Prescribing Information (PI) submitted on March 11, 2009 and further revised by DGP, the most recent version dated June 8, 2009 obtained from the eRoom on June 11, 2009
- Draft METOZOLV ODT MG (metoclopramide hydrochloride) orally disintegrating tablets Medication Guide (MG) submitted on March 11, 2009 further revised by DGP and provided to DRISK on June 16, 2009.

3 BACKGROUND

METOZOLV ODT (metoclopramide hydrochloride) orally disintegrating tablets is indicated for:

- **Symptomatic Gastroesophageal Reflux:**
METOZOLV ODT is indicated as short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux (GERD) who fail to respond to conventional therapy.
- **Diabetic Gastroparesis (Diabetic Gastric Stasis):**
METOZOLV ODT is indicated for the relief of symptoms associated with acute and recurrent diabetic gastric gastroparesis (gastric stasis).

DGP informed the Applicant that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for METOZOLV ODT (metoclopramide hydrochloride) orally disintegrating tablets in a Complete Response (CR) letter dated February 26, 2009, due to the serious risk of Tardive Dyskinesia (TD). The only elements of the REMS will be a MG and a timetable of submission of assessments of the REMS. The Applicant submitted a Complete Response (CR) on March 11, 2009 in response to the Agency's CR letter on February 26, 2009. The submission includes a proposed REMS for METOZOLV ODT (metoclopramide

hydrochloride) orally disintegrating tablets with updated labeling, including a proposed MG. The REMS is currently under review by DRISK, and will be provided to DGP under separate cover.

The Reference Listed Drugs for this product are Reglan (metoclopramide) Tablets (17-854) and Reglan ODT (metoclopramide) orally disintegrating tablets (NDA 21-793).

4 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

Content and formatting revisions are made to ensure that the information is legible, clear, and patient-friendly. Patient Information that is well designed and clearly worded can help to maximize patient use and understanding of important safety information that is presented.

The draft MG submitted by the Applicant has a Flesch Kincaid grade level of 7.8, and a Flesch Reading Ease score of 58.8%. DGP further revised the proposed MG to make it consistent with the revisions agreed to by DGP and DRISK for other MGs in the class. The revised MG has a Flesch Kincaid grade level of 7.3, and a Flesch Kincaid Reading Ease score of 62.3%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The MG reading scores as revised by the review division are acceptable.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI and with the MGs for other products in the class.
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***. We are providing the review division a marked-up and clean copy of the revised MG. All future relevant changes to the PI should also be reflected in the MG.

5 CONCLUSIONS AND RECOMMENDATIONS

1. Consistently use Metozolv ODT or Metozolv throughout the MG. Also, for the name of the product, consistently use all caps, (METOZOLV) or mixed upper and lower case (Metozolv). For purposes of our review, we have used “Metozolv ODT”.
2. We made the language in the section “What is Metozolv ODT?” consistent with the language recommended in our review of the MG for Reglan Tablets. Symptoms related to the indications are not included in this PI; therefore, they are not included in the MG.
3. In the section “What should I tell my doctor before taking Metozolv ODT?”:
 - Based on input from the Maternal Health Team, we are no longer referring to pregnancy and breastfeeding as medical conditions in patient labeling. We have worded this section according to our new template language for this section. The MGs for the other products in the class should be revised accordingly.
 - Reglan ODT contains aspartame and we include a bullet under “What should I tell my doctor before taking Reglan ODT” for phenylketonuria. DGP should clarify if a similar bullet is needed in this MG since it contains Acesulfame Potassium. We do not note any information about this in the PI.
 - Under “Tell your doctor about all the medicines you take...”: antipsychotic and neuroleptic drugs are listed in section 7.5 of the Meotozolv ODT PI but are not included in the Reglan or Reglan ODT PIs. DGP should clarify how to convey or what information if any about neuroleptic drugs should be added here. This is not a term common to most people. We have added a bullet for anti-psychotic medicines.
 - Revise the language in the second to the last paragraph of the section in the other MGs in the class so that it is in active voice as stated here:

“Ask your doctor or pharmacist if you are not sure if your medicine is listed above.”
4. We revised the language in the section “How should I take Metozolv ODT to be consistent with the language in Reglan ODT with the exception of the last bullet which has been added to this MG to be consistent with the Dosage and Administration section of the PI. In the added first bullet, if “melts” is not the correct term, DGP should revise this.
5. We revised the bullet “If you take too much...” so that it is consistent with the language in the Reglan ODT MG.
6. In the section “What should I avoid while taking Metozolv ODT?” consider adding the statement “TRADENAME may cause sleepiness” at the beginning of the bullet in the other MGs for the class.
7. In the section “What are the possible side effects of Metozolv ODT?”
 - Regarding the bullet for “Parkinsonism,” please be sure that the last statement in the bullet has been added to the MGs for all products in the class. The Reglan ODT MG accessed in the eRoom on June 18, 2009 and dated May 15, 2008 does not contain this language.

- We agree that information about high blood pressure should be included in the MG. It is in the Warnings and Precautions section of the PI for Metozolv ODT and the Precautions section of the PI for the other product PIs. This bullet should be added to the MGs for the other products in the class. Although patients may not know if their blood pressure is increased, they should be informed that it can occur.
 - We added a bullet to convey fluid retention and volume overload. A bullet should be added to the MGs for the other products in the class to convey fluid retention and fluid overload. This information is in the Warnings and Precautions section of the PIs for other products in the class.
 - We deleted the bullet for “Withdrawal symptoms” and placed information related to symptoms after stopping Metozolv ODT at the end of the information about common side effects to be consistent with placement in the MGs for other products in the class.
 - Under “the most common side effects of Metozolv ODT are:” some of the common side effects noted in the Reglan ODT MG do not appear in the Metozolv ODT PI. The list below reflects the common side effects (>2%) listed in the Highlights section and section 2.1 of the Metozolv ODT PI.
8. Section 17 of the PI should be expanded to include a statement that healthcare providers should review the MG with the patient, as well as to provide the information needed to counsel patients about taking Metozolv ODT. Consult the SEALD team regarding the requirement of:
- a statement at the beginning of Section 17 referencing the MG, such as “See FDA-approved patient labeling (Medication Guide).
 - if the MG will be part of section 17, then it should be included as a subsection, such as section 17.x.
 - adding the MG to the Table of contents for section 17 if it will be included at the end of the PI.

Please let us know if you have any questions.

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/s/

Sharon Mills
6/21/2009 08:18:30 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
6/22/2009 09:32:54 AM
DRUG SAFETY OFFICE REVIEWER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: June 16, 2009

To: Maureen Dewey, Regulatory Project Manager
Kristen Everett, Safety Regulatory Project Manager
Tamara Johnson, MD, MS, Medical Officer
Division of Gastroenterology Products (DGP)

From: Shefali Doshi, Regulatory Review Officer
Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Robert Dean, DTC Group Leader
Lisa Hubbard, Acting Professional Group Leader
DDMAC

Jodi Duckhorn, Lead Social Science Analyst, OSE
Sharon Mills, OSE

Subject: DDMAC labeling comments for Metozolv™ ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets
NDA 22-246

DDMAC has reviewed the proposed product labeling (PI and Medication Guide) submitted for consult to DDMAC on June 8, 2009, for Metozolv™ ODT (metoclopramide hydrochloride) Orally Disintegrating Tablets [Metozolv].

The PI version that served as the basis for this review was obtained via the DGP eRoom on June 11, 2009, and is titled, "NDA 22-246 Metozolv ODT label Agency revised 06-08-09.doc." Our comments on the proposed Medication Guide are based on the document that was attached to the June 8, 2009, DGP consult request to DDMAC.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions on the comments for the PI, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

If you have any questions on the comments for the Medication Guide, please contact Shefali Doshi at 301.796.1780 or Shefali.Doshi@fda.hhs.gov.

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/s/

Shefali Doshi
6/16/2009 09:41:36 AM
DDMAC CONSUMER REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 17, 2009

To: Donna Griebel, MD, Director
Division of Gastroenterology Products

Through: Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis
(DMEPA)

From: Laura Pincock, PharmD, Acting Team Leader
Division of Medication Error Prevention and Analysis
(DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Metozolv ODT (Metoclopramide) Orally Disintegrating
Tablets

Application Type/Number: NDA # 22-246

Applicant/sponsor: Wilmington Pharmaceuticals

OSE RCM #: 2008-1946

1 INTRODUCTION

The Division of Medication Error Prevention and Analysis (DMEPA) completed a review of the labels and labeling for Metozolv ODT in OSE Review# 2008-1946 dated June 10, 2009, in which we made recommendations regarding the proposed labels and labeling. Revised labels and labeling were submitted on June 18, 2009 and July 2, 2009.

2 MATERIAL REVIEWED

DMEPA reviewed our labeling review for Metozolv ODT signed on June 10, 2009 (OSE Review# 2009-1946). DMEPA also reviewed the revised Metozolv ODT carton labeling submitted on June 18, 2009 and July 2, 2009. See Appendices A through C for images.

- Metozolv ODT Retail Carton Labeling (5 mg and 10 mg)
- Metozolv ODT Professional Sample Carton Labeling (5 mg and 10 mg)
- Metozolv ODT Blister Pack Sleeve (5 and 10 mg)

3 DISCUSSION AND RECOMMENDATIONS

3.2.1 CARTON LABELING

DMEPA reviewed the Applicant's carton labeling for the 5 mg and 10 mg strengths of Metozolv ODT, which were revised according to our previous recommendations. They have addressed all of our concerns on the carton labeling, thus we have no further comments on the carton labeling.

3.2.2 BLISTER SLEEVE

DMEPA notes that the Applicant has proposed use of a new blister sleeve to accommodate CMC's direction that they need to use '(metoclopramide HCl) orally disintegrating tablet' rather than '(metoclopramide HCl) tablet' on the blister pack. DMEPA had not previously reviewed the blister sleeve. Wilmington states that the blister sleeve is needed to accommodate the additional wording. The blister sleeve is permanently affixed to the blister pack, and the blister pack backing will now only contain the lot number of the tablet batch. In an email from the Applicant on June 23, 2009, the Applicant states that each patient will be given a complete blister sleeve (10 tablets), or multiple sleeves depending on the quantity prescribed, and that no individual blister units will be dispensed.

Contrary to what the Applicant states, DMEPA has concerns that patients or institutions will cut or otherwise separate the blister pack backing from the blister sleeve to dispense or separate out individual tablets. On the sample provided to us, we were able to tear down and reveal the entire package of ten tablets. Since the blister pack backing no longer contains any identifying information such as the proprietary name, established name, and strength, it subsequently may be difficult to identify the tablets if removed from the blister sleeve at a future date. The Applicant should add the proprietary name, established name, and strength (as previously printed on the blister backing and discussed in our June 10, 2009 review) to the blister backing for safety reasons so that if someone does separate a tablet from the blister pack, the tablet will be identifiable.

The strength (5 mg or 10 mg) on the blister sleeve lacks prominence and is not immediately adjacent to the proprietary and established names. The strength should be prominently displayed and immediately follow the proprietary and established names of the product.

Additionally, we recommend that the blister sleeve be revised to state that 'each tablet contains X mg'. It is important that patients understand that the strength is specified per tablet. Patients

could be misled into thinking that the entire blister package comprises a dose resulting in dosing errors.

We note that the blister sleeve lacks a net quantity statement. The net quantity statement is important so that healthcare practitioners and patients can easily determine the contents of the blister sleeve (e.g., 10 orally disintegrating tablets). Additionally, DMEPA is unable to determine a location for the prescription label to be placed on the blister pack. If a pharmacy attempts to place a pharmacy label on the Metozolv ODT blister sleeve in the current format, it will cover several of the tablet blisters or the important information on the blister sleeve. Patients will attempt to remove the label to reach the tablets or may otherwise be unable to use them.

Finally, the Applicant has stated that two medication guides will be included in each box of Metozolv ODT (10 blister sleeves of 10 tablets). DMEPA does not believe that this number of medication guides is sufficient with the new packaging configuration, as Metozolv ODT will be dispensed in multiples of blister sleeves (10 tablets). Although a typical 30 day supply of Metozolv ODT will be 100-120 tablets depending on the prescribed dosage frequency, there are instances in which it could be used less frequently or for a shorter duration in which case two medication guides per 100 count carton would not be sufficient.

4 CONCLUSION

4.1 COMMENTS TO THE DIVISION

In our June 10, 2009 review, DMEPA deferred to CMC for the final decision on whether the Applicant should spell out the complete dosage form “Orally Disintegrating Tablets” on the blister card. The Applicant stated there is limited space on the blister card and has proposed use of a blister sleeve pack instead to provide all the necessary information. DMEPA has safety concerns with this proposal, due to the potential for the blister pack to be cut into separated tablets which would not contain any identifying information on each blister. Thus for safety reasons, the Applicant should include the text on the blister pack backing.

If you have further questions or need clarifications, please contact Phuong Nina Ton, OSE Regulatory Project Manager, at 301-796-1648.

4.2 COMMENTS TO THE APPLICANT

4.2.1 CARTON LABELING

The Applicant has satisfactorily revised the carton labeling per our June 10, 2009, review.

4.2.2 BLISTER SLEEVE

1. A net quantity statement (e.g., 10 orally disintegrating tablets) should be added to each blister sleeve.
2. The blister sleeve should contain a location for the prescription label to be placed so that it does not cover any of the tablet blisters or any of the important information on the blister sleeve.
3. Increase the size of the strength (e.g., 5 mg) to increase its prominence and relocate the strength adjacent to the proprietary and established names.
4. The blister sleeve should also state that ‘each tablet contains X mg’. The word ‘each’ is especially important since each individual blister is no longer labeled as containing 5 mg or 10 mg of Metozolv ODT.

5. The Applicant should provide sufficient medication guides in the box of 100 tablets (more than two medication guides), because the blister sleeves are dispensed in multiples of ten (10 blister sleeves of 10 tablets). Two medication guides may not be a sufficient number if Metozolv ODT is prescribed with less frequent dosing or for a shorter treatment duration in which case the two medication guides per 100 count carton may not be sufficient to ensure that every patient receives a medication guide.

4.2.3 BLISTER BACKING

1. Add the proprietary name, established name, and strength (as previously printed on the blister backing) back to the blister backing so that if someone does separate a tablet or blister strip from the blister pack, the tablet will be identifiable for safety reasons.

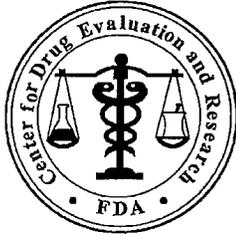
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Laura Pincock
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DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/17/2009 04:59:05 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 13, 2009

To: Donna Griebel, MD, Director
Division of Gastroenterology Products

Through: Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis
(DMEPA)

From: Laura Pincock, PharmD, Acting Team Leader
Division of Medication Error Prevention and Analysis
(DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Metozolv ODT (Metoclopramide Orally Disintegrating)
Tablets

Application Type/Number: NDA # 22-246

Applicant/sponsor: Wilmington Pharmaceuticals

OSE RCM #: 2008-1946

1 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the blister labels and carton labeling submitted as part of the Complete Response submission on March 10, 2009 (see Appendix A and B). We have reviewed the blister labels and carton labeling in two previous reviews (OSE # 2008-1148 dated October 24, 2008 and OSE # 2008-1946 dated February 6, 2009).

2 RECOMMENDATIONS

Our evaluation noted areas where information on the blister labels and carton labeling can be improved to minimize the potential for medication errors. We provide recommendations on the blister labels and carton labeling in Section 2.2 *Comments to the Applicant*. We request the recommendations in Section 2.2 be communicated to the Applicant prior to approval.

2.1 COMMENTS TO THE DIVISION

DMEPA noted in a previous review of the blister labels and carton labeling (OSE # 2008-1946, dated February 6, 2009), that the complete dosage form “Orally Disintegrating Tablets” should be spelled out on the blister labels. In their Complete Response, the Applicant has requested a small package exemption for the blister labels, due to the small size of the blister card. Thus, they have not spelled out the complete dosage form “Orally Disintegrating Tablets” on the blister card. DMEPA will defer to CMC for the final decision on this issue.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Phuong Nina Ton, OSE Regulatory Project Manager, at 301-796-1648.

2.2 COMMENTS TO THE APPLICANT

2.2.1 CARTON LABELING

1. The equivalency statement on the carton labeling for both strengths should be corrected to accurately state the milligrams of metoclopramide hydrochloride. As currently stated, this statement incorrectly reads on the 5 mg strength: “*contains 5 mg metoclopramide hydrochloride equivalent to 5 mg metoclopramide”. For the 5 mg strength, the amount of metoclopramide hydrochloride should be 5.91 mg and for the 10 mg strength, it should be 11.82 mg.
2. Although your labels and labeling contain the required statement alerting the dispenser to provide the Medication Guide with the product for all strengths and formulations, we recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
 - a. “Dispense the enclosed Medication Guide to each patient.” or
 - b. “Dispense the accompanying Medication Guide to each patient.”

3. Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:
 - a. A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
 - b. A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

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/s/

Laura Pincock
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DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/10/2009 04:14:45 PM
DRUG SAFETY OFFICE REVIEWER



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: February 6, 2009

To: Donna Griebel, MD
Director, Division of Gastroenterology Products

Through: Kellie Taylor, PharmD, MPH, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Laura Pincock, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review for Metozolv ODT

Drug Name(s): Metozolv ODT (Metoclopramide Orally Disintegrating) Tablets
5 mg and 10 mg

Application Type/Number: NDA # 22-246

Applicant: Wilmington Pharmaceuticals

OSE RCM #: 2008-1946

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EXECUTIVE SUMMARY

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, we noted the lack of presentation of the entire proprietary name on the same line, the presentation of the established name, and the lack of differentiation between the two strengths (5 mg and 10 mg). These risks can be addressed and mitigated prior to drug approval. We provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Gastroenterology Products for assessment of the container label, carton, and insert labeling to identify areas that could lead to medication errors. The container labels, carton, and insert labeling were previously reviewed by DMEPA in OSE Review #2008-1148, dated October 24, 2008.

The proposed proprietary name, Metozolv ODT, was previously reviewed by DMEPA (OSE Consult # 2008-305, dated July 18, 2008) without objection. A final review of the proposed proprietary name, Metozolv ODT will be provided under separate cover in a forthcoming review (OSE Review # 2008-1910).

1.2 PRODUCT INFORMATION

Metozolv ODT is the proposed name for metoclopramide orally disintegrating tablets. Metozolv ODT is a prokinetic agent indicated for the management of diabetic gastroparesis and gastroesophageal reflux disease.

The dosage for diabetic gastroparesis is 10 mg orally at least 30 minutes before each meal and at bedtime up to 4 times per day. The usual dose for gastroesophageal reflux disease is 10 mg to 15 mg orally up to four times a day at least 30 minutes before each meal and at bedtime. Doses may vary depending upon the symptoms being treated and the clinical response. If symptoms only occur intermittently or at specific times of the day, Metozolv ODT may be used in single doses up to 20 mg prior to the provoking situation rather than continuous treatment.

The maximum dose for Metozolv ODT is 60 mg per day for gastroesophageal reflux disease and 40 mg per day for diabetic gastroparesis. Metozolv ODT will be available as 5 mg and 10 mg orally disintegrating tablets in foil-backed unit dose blister packs of 10 tablets. Each carton will contain 10 blister cards for a total of 100 orally disintegrating tablets per carton. Metozolv ODT should be stored at controlled room temperature.

2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment (see 2.1 Container Label, Carton and Insert Labeling Risk Assessment). The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may

cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 CONTAINER LABEL AND CARTON LABELING

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton labeling and container label communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because the Division of Medication Error Prevention and Analysis staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The medication error prevention staff uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted blister container and carton labeling on September 11, 2008 for review (see Appendix A, B):

- Blister label: 5 mg (10 count sample, 100 count sample, 100 count commercial)
- Blister label: 10 mg (10 count sample, 100 count sample, 100 count commercial)
- Carton labeling: 5 mg (10 count sample, 100 count sample, 100 count commercial)
- Carton labeling: 10 mg (10 count sample, 100 count sample, 100 count commercial)
- Prescribing Information (no image)

3 RESULTS

Upon review of the container label and carton labeling, the Division of Medication Error Prevention and Analysis notes the following areas of needed improvement.

3.1 BLISTER LABELS

The complete dosage form “Orally Disintegrating Tablets” does not appear on the blister labels. The modifier ODT does not appear as part of the proprietary name (e.g., Metozolv ODT).

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3.2 CARTON LABELING

The product strengths are presented in the same font color for both strengths.

The color scheme of the cartons for both strengths (5 mg and 10 mg) are primarily red and blue, and as a result very similar.

The modifier ODT does not appear as part of the proprietary name (e.g., Metozolv ODT).

4 DISCUSSION

Our analysis of the Proprietary name, container labels and carton labeling noted several areas of needed improvement. They are as follows:

4.1 LACK OF COMPLETE DOSAGE FORM ON THE BLISTER LABELS

The complete dosage form, Orally Disintegrating Tablets, does not appear on the blister labels. The blister labels contain the abbreviation “ODT” adjacent to the word tablets. However, this descriptor is not an approved abbreviation for use in the established name to designate the finished dosage form. This presentation is misleading because it does not accurately reflect the product as an orally disintegrating tablet. As presented, the “ODT” is not part of the proprietary name and thus does not differentiate this product from the existing metoclopramide oral tablet formulation. It is important for healthcare providers and patients to be able to distinguish this product from currently marketed formulations of Metoclopramide tablets. It is also important for healthcare practitioners and patients to be able to differentiate between the two dosage forms to prevent medication errors.

4.2 PLACEMENT OF ODT IN THE PROPRIETARY NAME

The proprietary name for this product is Metozolv ODT. However, “ODT” does not appear on the same line as Metozolv and is not prominent so it does not appear to be part of the proprietary name. “ODT” must be conveyed adjacent to the root name Metozolv, appearing in the same font as Metozolv, to correctly communicate the full proprietary name. It is important that the name be prominently featured as “Metozolv ODT” because it is the key feature that will distinguish this product from currently marketed formulations of Metoclopramide tablets. The proprietary name should be communicated as Metozolv ODT on all labels and labeling, with all words on the same line.

4.3 INADEQUATE DIFFERENTIATION OF STRENGTH

The applicant has attempted to differentiate the carton labeling for the 5 mg and 10 mg strength by blocking the entire carton (e.g., blue for 10 mg and pink for 5 mg). However, the text used for both strengths is presented in the same font color which decreases the effectiveness of the color differentiation. DMEPA noted this color presentation in our previous review, and maintains that it would be better if the applicant carried the color block to the strength. DMEPA is also concerned that the two carton strengths (5 mg and 10 mg), make use of the same colors (red and blue) and have inverted the color schema for each strength. As a result the two carton strengths are not well differentiated and are not as distinguishable from each other as they could be.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the information presented lacks prominence, is misleading and may introduce vulnerability to confusion that could lead to medication errors. Specifically, we noted the lack of presentation of the entire proprietary name on the same line, the presentation of the established name, and the lack of differentiation between the two strengths (5 mg and 10 mg). The risks we have identified can be addressed and mitigated prior to drug approval. We provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

The Division of Medication Error Prevention and Analysis would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

5.2 COMMENTS TO THE APPLICANT

Based upon our FMEA of the labels and labeling, DMEPA identified several areas of needed improvement. We request you revise your labels and labeling as follows:

5.2.1 *Blister Label and Carton Labeling*

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. Also, revise so that the complete dosage form immediately follows the established name, for example:

Metozolv ODT
(Metoclopramide) Orally Disintegrating Tablets
XX mg

5.2.2 *Blister Label*

Spell out the complete dosage form “Orally Disintegrating Tablets” on the blister labels. We note that this recommendation is reflected in section 5.2.1 above.

5.2.3 *Carton Labeling*

1. Differentiate the product strengths by boxing, highlighting, using a different color font, or some other means.
2. Consider using a different color schema for one of the strengths (not just red and blue) to improve the distinguishability between the two strengths, thereby decreasing the potential for a selection error.

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 24, 2008

To: Donna Griebel, MD
Director, Division of Gastroenterology Products

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, Pharm D, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Diane C. Smith, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review for Metozolv ODT

Drug Name(s): Metozolv ODT (Metoclopramide Orally Disintegrating) Tablets
5 mg and 10 mg

Application Type/Number: NDA # 22-246

Applicant: Wilmington Pharmaceuticals

OSE RCM #: 2008-1148

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EXECUTIVE SUMMARY

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. Specific improvements include the presentation of the entire proprietary name on the same line as well as the inclusion of the complete dosage form statement on the blister label and carton labeling. Additionally, differentiation of the product strengths from one another and including the NDC number on the principle display panel. These risks can be addressed and mitigated prior to drug approval. We provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Gastroenterology Products for assessment of the container label, carton, and insert labeling for the product "Metozolv ODT" (NDA-22-246) to identify areas that could lead to medication errors. DMEPA reviewed the proprietary name under OSE Review #2008-305, and had no objection to the proposed proprietary name, Metozolv ODT, for this product.

1.2 PRODUCT INFORMATION

Metozolv ODT (Metoclopramide Orally Disintegrating Tablets) is a prokinetic agent indicated for management of diabetic gastroparesis and gastroesophageal reflux disease. The dosage for diabetic gastroparesis is 10 mg by mouth up to four times a day, at least 30 minutes before each meal and at bedtime. The dosage for gastroesophageal reflux disease is 10 mg to 15 mg by mouth up to four times a day, at least 30 minutes before each meal and at bedtime. Metozolv ODT will be available in a 5 mg and 10 mg orally disintegrating tablets in foil-backed blister packs of 10 tablets. Each carton will contain 10 blister cards for a total of 100 orally disintegrating tablets per carton.

2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment (see 2.1 Container Label and Carton and Insert Labeling Risk Assessment). The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

2.1 CONTAINER LABEL AND CARTON LABELING

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton labeling and container label communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because the Division of Medication Error Prevention and Analysis staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The medication error prevention staff uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted insert and carton labeling on May 20, 2008 and the blister labels were submitted on June 9, 2008, for review (see Appendix A, B):

- Blister label: 5 mg and 10 mg
- Carton labeling: 5 mg and 10 mg 100 tablet count
- Prescribing Information (no image)

3 RESULTS

Upon review of the container label and carton labeling, the Division of Medication Error Prevention and Analysis note the following areas of needed improvement.

3.1 ALL LABELS AND LABELING

The complete dosage form “Orally Disintegrating Tablets” does not appear on the labels and labeling.

The modifier ODT does not appear as part of the proprietary name.

3.2 CARTON LABELING

We note the location of the NDC number is not in accordance with 21 CFR 207.35(b)(3)(i) which states “The NDC number shall appear prominently in the top third of the principal display panel of the label on the immediate container and of any outside container or wrapper”.

The established name is presented in a light font which is not in accordance with 21 CFR 201.10 (g)(2) which states: “the established name shall have a prominence commensurate with the

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features”.

The graphic used in the second ‘o’ in the proprietary name interferes with the readability of the name.

The product strengths are presented in the same font color for both strengths.

4 DISCUSSION

Our analysis of the Proprietary name, container labels and carton labeling noted several areas of needed improvement.

4.1 PLACEMENT OF ODT IN THE PROPRIETARY NAME

The proprietary name for this product is Metozolv ODT. However, the “ODT” portion of the name does not appear on the same line as Metozolv and is not a prominent. The “ODT” portion of the name must be emphasized because it is the key feature that will distinguish this product from currently marketed formulations of Metoclopramide tablets. It is important for healthcare practitioners and patients to be able to differentiate between the two dosage forms to prevent medication errors.

Additionally, the placement of the “ODT” on the blister label is misleading because it does not accurately reflect the product as an orally disintegrating tablet. The “ODT” name suffix is placed before the word tablet. This descriptor is not an approved abbreviation for use in the established name to designate the finished dosage form it is a descriptor of the proprietary name.

4.2 USE OF THE GRAPHIC IN PROPRIETARY NAME

We note that the Applicant has chosen to use a graphic as the second “o” in the proprietary name on the carton labeling. This graphic interferes with the readability of the name. Additionally, as presented the proprietary name may be misinterpreted as two different words (i.e., Metoz LV).

4.3 PLACEMENT OF NDC NUMBER

The NDC number is not presented in accordance with the regulations. If the NDC number is not placed in conjunction with the barcode then it is required to appear prominently in the top third of the principal display panel of the label on the immediate container and any of the outside container and wrapper.

4.4 INADEQUATE DIFFERENTIATION OF STRENGTH

The applicant has attempted to differentiate the carton labeling for the 5 mg and 10 mg strength by blocking the entire carton (e.g., blue for 10 mg and pink for 5 mg). However, the text used for the strengths is presented in the same font color which decreased the effectiveness of the color differentiation. The current presentation may be a source of confusion. It would be better if the applicant carried the color block to the strength.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the information presented lacks prominence, is misleading and may introduce vulnerability to confusion that could lead to medication errors. The risks we have identified can be addressed and mitigated prior to drug approval. We provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

Based upon our assessment of the Metozolv ODT blister label, carton and insert labeling we have identified areas of needed improvement. We recommend implementation of the following label and labeling revisions as outlined in section 5.2 below.

The Division of Medication Error Prevention and Analysis would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

5.2 COMMENTS TO THE APPLICANT

Based upon our FMEA of the labels and labeling, DMEPA identified the following areas of needed improvement.

5.2.1 *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. Also, revise so that the complete dosage form immediately follows the established name, for example:

Metozolv ODT
(Metoclopramide) Orally Disintegrating Tablets
XX mg

5.2.2 *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. Relocate the NDC number to appear in accordance with 21 CFR 207.35(b)(3)(i).

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/s/

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