CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-246

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, MD, MPH Deputy Director for Safety Division of Gastroenterology Products Office of New Drugs III Center for Drug Evaluation and Research
Subject	Division Director (Deputy) Summary Review
NDA/BLA # **Supplement #**	NDA 22-246
Applicant Name	Wilmington Pharmaceuticals, INC.
Date of Re-Submission	March 13, 2009
PDUFA Goal Date	September 11, 2009
Proprietary Name / **Established (USAN) Name**	Metozolv (metoclopramide hydrochloride) Orally Disintegrating Tablet
Therapeutic Class	Dopamine receptor antagonist
Dosage Forms / Strength	5 mg and 10 mg tablets
Dosing and Administration	**Gastroesophageal Reflux** : 10 to 15 mg dose up to four times daily at least 30 minutes before eating and at bedtime **Diabetic Gastroparesis (Diabetic Gastric Stasis)** 10 mg dose four times daily at least 30 minutes before eating and bedtime for two to eight weeks.
Proposed Indication(s)	Metozolv is indicated for : • Relief of Symptomatic Gastroesophageal Reflux • Diabetic Gastroparesis (Diabetic Gastric Stasis)
Action/Recommended Action:	**Approval**

1. Introduction

(Note: *this memo addresses the sponsor response to the deficiencies listed in the Complete Response Letter to the original submission [received March 13, 2009]. My original review [February 26, 2009] is appended which addresses all other aspects of the review found to be satisfactory at the time of the original action.*)

Metoclopramide is a dopamine D2 receptor antagonist and is also a mixed 5-hydroytryptamine (5-HT_3) /5-HT4 receptor antagonist. Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. It increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter, and has little, if any, effect on the motility of the colon or gallbladder.

In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide produce dose-related increases in LESP. Effects begin at about 5 mg and increase through 20 mg (the largest dose tested). The increase in LESP from a 5 mg dose lasts about 45 minutes and that of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

Dopamine readily crosses the blood-brain barrier. The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by agents like l-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

Similar to the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions such as dystonic reactions, Parkinsonian-like symptoms and tardive dyskinesia. Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with transient fluid retention.

2. Background

Regulatory History:
This application was originally submitted November 5, 2007. On January 3, 2008 FDA received notice that Wilmington Pharmaceuticals was withdrawing their application. This was due to continuing discussions with the FDA regarding the

Listed Drug for the 505(b)(2) application. The reason which necessitated withdrawal was that Paragraph IV Certifications were not permitted to be submitted as amendments to the application. NDA 22-246 was resubmitted on January 29, 2008. On October 22, 2009 FDA received a major amendment which extended the user fee goal date to February 27, 2009. This first application was given a Complete Response action on February 26, 2009.

Listed drugs in this 505(b)(2) application include NDA 17-854 (Reglan Tablets) and refers to NDA 21-793 (Reglan ODT) as a pharmaceutical equivalent. Currently, Reglan ODT is not marketed.

This current submission from Wilmington Pharmaceuticals, received March 13, 2009, was filed as a complete response and was given a PDUFA goal date of September 11, 2009. It was determined that a boxed warning and Medication Guide were needed, invoking the FDA Amendments Act of 2007 Risk Evaluation and Mitigation Strategy requirement. The need for a Medication and Guide and boxed warnings for tardive dyskinesia with chronic treatment are stated in my original review recommending a Complete Response Action (February 26, 2009), which is appended to this memo. This issue is considered a class labeling issue and other pharmaceutical manufacturers of these products were notified that a Medication Guide and REMS were required at time same time as the original Complete Response action for Metozolv.

Other outstanding issues included finalization of the labeling (especially the wording relating to the class labeling safety issue), Medication Guide, agreed upon stability expiration dating and carton/container labeling.

Requested indication: the applicant requests the same indications granted Reglan Tablets (NDA 17-854): 1.) Symptomatic Gastroesophageal Reflux for adults as short-term therapy with documented gastroesophageal reflux who fail to respond to conventional therapy; 2.) Diabetic Gastroparesis (Diabetic Gastric Stasis). Reglan Tablets were approved in the early 1980's and are currently marketed with the old package insert format.

3. Labeling

- **Clinical Pharmacology Labeling Modifications:**
  During this cycle review, recommendations were made to further describe the tablet disintegration time and food-effect statement in the dosage and Administration Section. (b) (4) Finally, there was an addition in Section 8.6, Other Special Populations, to clarify the use of Metozolv in the setting of liver disease (b) (4) These changes were acceptable to the team and sponsor and are reflected in the final label attached to the approval letter.

- **Medication Guide**

  Wilmington Pharmaceuticals proposed some changes to the requested Medication Guide. The new review team took those recommendations and reconsidered the literature and the recommendations from the original review team. The team recommended that a discussion of potential sub-group risk factors would be more appropriately placed in the Warning Section of the label due to the fact that the literature did not readily differentiate these risk factors. This issue could be more fully described in the Warning Section. After internal discussion and harmonization with class Medication Guides the review team agreed upon final labeling and Medication Guide. The Medication Guide, boxed warning and Warning Section regarding tardive dyskinesia was finalized and agreed upon by all manufactures of drugs in the metoclopramide class. The final version can be viewed by referring to the approval letter.

- **Carton and Container Labeling**

  The product will be packaged in aluminum blisters (10 tablets per blister card), with each blister card will be packaged in a blister sleeve). The art work for the blister sleeve and blister card was submitted on August 20, 2009.

  From the CMC prospective the blister sleeve labeling is acceptable. Due to space limitations, not all the information carried on the blister sleeve is included in the blister label, but it contains sufficient information to ensure that the product is identifiable based on the blister label, conforming to 21 CFR 201.10(i). Therefore, the carton/container labeling is acceptable.

4. Safety Update:

No new safety issues were seen in this resubmission.

5. Decision/Action/Risk-Benefit Assessment

- **Regulatory Action:** I recommend that this NDA receive an approval with the agreed upon Medication Guide only Risk Evaluation and Mitigation Strategy (REMS), and final labeling as reflected in the approval letter.

- **Post Marketing Requirements/ Commitments:** None

- **PREA** – Note that PREA does not apply to this 505(b)(2) application.

- Expiration dating is acceptable for a 30 month expiry according to CMC review.

I have appended my original Complete Response Recommendation Memo for convenience of the reader. Please refer to for complete discussion of Benefit/Risk Assessment.

Material Reviewed/Consulted: OND Action Package	**Reviewer**
Medical Officer Review	F. Gibril (2/17/09)
Medical Team Leader Review	H. Ruyi (2/20/09)
Statistical Review	NA
Pharmacology Toxicology Review	T. Chakraborti (10/1/08)
Clinical Pharmacology Review	T. Gosh (11/3/08) K Estes (6/18/2009)
CMC Review	G. Holbert (1/30/09) J. Metcalfe (8/27/08) M. Kowblansky (9/24/09)
DSI Inspection Clinical Pharmacology site	C.T. Viswanathan (1/9/09)
OSE/ Epidemiology	K. Gelprin (6/27/08) OSE RCM: #2008-269
OSE/DRISK	S. Mills (5/29/2009, 6/21/09)
OSE/DDMAC	S. Doshi (6/16/2009)
OSE/Division of Medication Error Prevention Review	L. Pincock (2/6/09,5/4/09, 6/13/09, 7/17/09) Z. Oleszezuk (7/9/08)
SEALD	J. Delasko (11/13/08, 6/25/09)

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
SEALD=Study Endpoints and Label Development Division

Summary Review for Regulatory Action

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Subject	Division Director (Deputy) Summary Review
NDA/BLA # **Supplement #**	NDA 22-246
Applicant Name	Wilmington Pharmaceuticals, INC.
Date of Submission	January 29, 2008
PDUFA Goal Date	February 27, 2009
Proprietary Name / **Established (USAN) Name**	Metozolv (metoclopramide hydrochloride) Orally Disintegrating Tablet
Therapeutic Class	Dopamine receptor antagonist
Dosage Forms / Strength	5 mg and 10 mg tablets
Dosing and Administration	**Gastroesophageal Reflux** : 10 to 15 mg dose up to four times daily at least 30 minutes before eating and at bedtime **Diabetic Gastroparesis (Diabetic Gastric Stasis)** 10 mg dose four times daily at least 30 minutes before eating and bedtime for two to eight weeks.
Proposed Indication(s)	Metozolv is indicated for : • Relief of Symptomatic Gastroesophageal Reflux • Diabetic Gastroparesis (Diabetic Gastric Stasis)
Action/Recommended Action:	**Complete Response**

1. Introduction

Metoclopramide is a dopamine D2 receptor antagonist and is also a mixed 5-hydroytryptamine (5-HT_3) /5-HT4 receptor antagonist. Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. It increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter, and has little, if any, effect on the motility of the colon or gallbladder.

In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide produce dose-related increases in LESP. Effects begin at about 5 mg and increase through 20 mg (the largest dose tested). The increase in LESP from a 5 mg dose lasts about 45 minutes and that of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

Dopamine readily crosses the blood-brain barrier. The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by agents like l-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

Similar to the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions such as dystonic reactions, Parkinsonian-like symptoms and tardive dyskinesia. Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with transient fluid retention.

2. Background

Regulatory History:

This application was originally submitted November 5, 2007. On January 3, 2008 FDA received notice that Wilmington Pharmaceuticals was withdrawing their application. This was due to continuing discussions with the FDA regarding the Listed Drug for the 505(b)(2) application. The reason which necessitated withdrawal was that Paragraph IV Certifications were not permitted to be submitted as amendments to the application. NDA 22-246 was resubmitted on January 29, 2008. On October 22, 2009 FDA received a major amendment which extended the user fee goal date to February 27, 2009.

Listed drugs in this 505(b)(2) application include NDA 17-854 (Reglan Tablets) and refers to NDA 21-793 (Reglan ODT) as a pharmaceutical equivalent. Currently, Reglan ODT is not marketed.

Requested indication: the applicant requests the same indications granted Reglan Tablets (NDA 17-854): 1.) Symptomatic Gastroesophageal Reflux for adults as short-term therapy with documented gastroesophageal reflux who fail to respond to conventional therapy; 2.) Diabetic Gastroparesis (Diabetic Gastric Stasis). Reglan Tablets were approved in the early 1980's and are currently marketed with the old package insert format.

3. Chemistry and Manufacturing

The CMC review team recommended the following:

"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. However, labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is NOT recommended for approval until the pending issues are resolved." Chemistry did not recommend any PMR/PMCs.

EES assessment was found acceptable 2/7/8 (S. Adams)
EA Categorical exclusion was granted 7/31/08 (G. Holbert)

"The applicant's request for a waiver of *in vivo* bioavailability studies for the 5 mg strength is granted under the provisions of 21 CFR 320.22(d)(2) based on bioequivalence of the 10 mg tablet with the Reference Listed Drug (Reglan); formulation proportionality between the 5 mg and 10 mg strengths; both strengths are the same dosage form made from a common batch formula; and *in vitro* dissolution testing."

"Patrick Marroum, Ph.D., ONDQA Biopharmaceutics Expert has concurred with our conclusion."

Finally, it was noted that the current guidance regarding the definition of Orally Disintegrating Tablet states that the *in vitro* disintegration time be approximately 30 seconds or less. This was true of Metozolv, so according to the guidance the term would be applicable to this product based upon the *in vitro* testing. (See Clinical Pharmacology Section for additional discussion of this issue regarding *in vivo* testing).

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the submission. The outstanding deficiencies regarding professional labeling and carton and container labeling will need to be resolved prior to approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

The review team provided the following conclusion:

"This NDA was submitted as a 505 (b)(2) application. The sponsor did not conduct any nonclinical studies with metoclopramide. The sponsor is relying on the Agency's previous findings of safety and efficacy for the reference listed drug (RLD), Reglan® Tablets. There is no difference in the strength, dose, route of administration, clinical indication, or duration of dosing of Reglan Tablets and Metozolv ODT."

"From a nonclinical standpoint, this NDA is recommended for approval for the proposed use." Recommendations for modifications of the proposed label were made to the sponsor.

I concur with the conclusions reached by the pharmacology/toxicology reviewer. Resolution of the labeling modifications must be resolved prior to an approval action.

5. Clinical Pharmacology

The clinical pharmacology reviewer made the following written recommendations:

"NDA 22-246, METZOLV® ODT (metoclopramide orally disintegrating tablets) 5 and 10 mg, submitted on January 27, 2007 has been reviewed by Office of Clinical Pharmacology /Division of Pharmaceutical Evaluation III (OCP/DCP III). 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. The biowaiver for the 5 mg strength is being reviewed by ONDQA."

In support of this NDA, the sponsor submitted one pilot study and two pivotal studies. The pivotal studies which were reviewed included:

- Study 10643701 - The Relative Bioavailability of Metoclopramide 10 mg Orally Disintegrating Tablets Compared to REGLAN® (metoclopramide) 10 mg Tablets (Schwartz Pharma) Under Fed and Fasted Conditions and;
- Study N 10743701:The Effect of Food on the Bioavailability of Metoclopramide 10 mg Orally Disintegrating Tablets and on its Relative Bioavailability with REGLAN® (metoclopramide) 10 mg Tablets (Schwartz Pharma).

These studies demonstrated bioequivalence under the fasted state. In study N 10743701, the AUC's were equivalent under fed conditions but the Cmax was approximately 24% lower for the test product after the high fat meal, therefore, not bioequivalent in the fed state. The bridge was acceptable in the fasted state.

The proposed dosing regimen for METZOLV® ODT is the same as Reglan® IR tablets and there is no new indication proposed for METZOLV® ODT.

The sponsor requested a waiver of the *in vivo* BA study for the 5 mg strength of

METZOLV® ODT based on the demonstrated bioequivalence of the 10 mg METZOLV® ODT to the Listed Drug together with the formulation proportionality between the 5 mg and 10 mg strengths. Chemistry has approved this waiver (see Chemistry section).

Finally, the issue regarding the use of the term Orally Disintegrating Tablet was discussed in light of the following *in vivo* information. In clinical trials (N=96), Metozolv ODT disintegrates on the tongue in approximately one minute with a range of 10 seconds to 14 minutes. (Mean ± SD = 76.8 ± 110.6 seconds; median = 53.5 seconds) METOZOLV ODT is designed to be taken without liquid; however, the effect on the pharmacokinetics of taking Metozolv ODT with liquid is unknown.

The pharmacology reviewer did not agree that "orally disintegrating tablet" was a good term to use for this formulation since in one case it took up to 14 minutes to dissolve completely in one case. However, during team meetings subsequent to formal submission of his final review recommendations, he agreed that if CMC found the term to be acceptable, and the applicant would describe the parameters as they appear in the above paragraph, then he would find the labeling acceptable for the final draft. According to the ODT guidance referred to by the CMC team; the *in vitro* data supports the use of ODT for this formulation.

I concur with the final conclusions reached by the clinical pharmacology reviewer during labeling team meetings as described above regarding the term ODT and description of time required for complete disintegration of the tablet. Resolution of the labeling modifications must be resolved prior to an approval action.

6. Clinical Microbiology

Product quality microbiological reviewer recommends approval of this application and no Phase IV studies. No deficiencies were identified.

7. Clinical/Statistical-Efficacy

There were no clinical efficacy studies submitted in this 505(b)(2) application. The sponsor applied for the currently approved indications listed in the Listed Drug REGLAN (metoclopramide) Tablets. These indications are: Relief of Symptomatic Gastroesophageal Reflux; Diabetic Gastroparesis (Diabetic Gastric Stasis).

It should be noted that the original approval of Reglan Tablets was in the early 1980's. At that time the available therapies for GERD were few. Today, there are many options, especially the highly effective proton pump inhibitors. The mechanism of action of the proton pump inhibitors is to reduce gastric acid, a different mechanism than metoclopramide, which acts by increasing motility and the lower esophageal sphincter pressure. The indication in full is as follows:

> "Symptomatic Gastroesophageal Reflux: reglan® tablets are indicated as short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy."

Thus, the current indication is not for first line therapy, which would most likely be a proton pump inhibitor. In addition, given the fact that this classes of drugs has a different mechanism of action from the acid modifiers, it may useful for patients for whom other GERD treatments are not effective.

There are no other approved therapies for diabetic gastroparesis. As such, such this indication is acceptable.

The medical reviewer and team leader agreed that these indications were appropriate at this time. *I am in agreement.*

8. Safety

- **Postmarketing data:**

During our review of this product the Office of Surveillance and Epidemiology performed a review of the safety of metoclopramide. This review focused on the serious neurological adverse events associated with long term exposure to metoclopramide. The Safety Issues Review Team determined that revisions to the warning section, a boxed warning and a Medication Guide were needed for this class of products. Thus, a class labeling was recommended for all of the metoclopramide products, which will include a boxed warning and a Medication Guide. This recommendation results in the need to request REMS elements for Metozolv ODT which will be a Medication Guide and a timetable for submission of assessments of the REMS. See Section 12 for more detail regarding the REMS Safety Issue.

In addition to the above review, the medical reviewer provided a review of the clinical trials in the safety section of the proposed label. It included the patients that were exposed to the to-be-marketed product in the pharmacokinetic studies. This revised table was sent to the sponsor during this NDA review cycle. It more accurately reflects the adverse events that were seen during these studies.

I am in agreement with these recommendations.

- **Proprietary Name Review:** The division of Medication Error Prevention reviewed the name, Metozolv (metoclopramide) ODT, and found it acceptable.

I agree with their conclusion.

- **Final labeling recommendations:**
Some important highlights are outlined here (see full label for more detail). It should be noted that the conversion of the innovator label to the PLR format for Metozolv will require additional discussions with the applicant during the next cycle.

(b) (4)

(b) (4)

[redacted]

- **REMS (Risk Evaluation Mitigation Strategy):**
  The GI Division recommends a REMS. The proposed REMS must include a Medication Guide and a time table for submission of REMS assessments.

  I concur with the REMS.

- **Advisory Committee Meeting**
  An Advisory Committee meeting was not held for this 505(b)(2) application.

9. Pediatrics

NA

10. Other Relevant Regulatory Issues

- **DSI Audits:** site inspection of clinical pharmacology studies is acceptable.
- **Financial Disclosure:** form submitted and acceptable.
- **SEALD:** provided written comments which were considered by the team during labeling discussions of the review team. This label represents conversion to the new PLR format as the Listed Drug is currently in the old format.

11. Labeling

- **Physician labeling:** It was recommended that the approved labeling for Metozolv include a box warning for the risk of tardive dyskinesia with use longer than 12 weeks and its relation to prolonged use.
- **Carton and immediate container labels:** The following will be transmitted in the CR letter:

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

5. 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".

- **Medication Guide:**
The review team determined that a Med Guide is required for this product. It is a currently outstanding deficiency. *I agree with this recommendation.*

12. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** I recommend that this NDA receive a complete response because of the outstanding safety issues which require resolution of final labeling, box warning, and submission of and agreement on the Risk Evaluation and Mitigation Strategy (REMS).

- **Risk Benefit Assessment:**
This is a 505(b)(2) application of oral metoclopramide. We agree that the current indications for GERD resistant to other therapies and diabetic gastric stasis are appropriate indications. While there are other products on the market for first-line treatment of GERD (proton-pump inhibitors), this product could be used as a last resort. At this time, we believe that it is appropriately labeled for this indication. There are no other approved therapies for diabetic gastric stasis. However, a review of the current use practices of metoclopramide products has determined that they are being utilized for a prolonged period of time, beyond the recommended 12 weeks. Tardive dyskinesia, a known serious adverse effect of the drug, is more likely to manifest in the patients who take it for a prolonged period of time. Thus, the OND and OSE review teams recommended strengthening the warnings and the addition of a boxed warning to this class of drugs and require a Medication Guide to ensure safe use of this drug.

- **Recommendation for Postmarketing Risk Evaluation Mitigation Strategy (REMS) Activities:**
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. The target action date is February 27, 2009. 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 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 reinstituted 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 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 Metozolv ODT will be a Medication Guide and a timetable for submission of assessments of the REMS. 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.

- **Recommendation for other Postmarketing Study Requirements:**

None

Material Reviewed/Consulted: OND Action Package	**Reviewer**
Medical Officer Review	F. Gibril (2/17/09)
Medical Team Leader Review	H. Ruyi (2/20/09)
Statistical Review	NA
Pharmacology Toxicology Review	T. Chakraborti (10/1/08)
Clinical Pharmacology Review	T. Gosh (11/3/08)
CMC Review	G. Holbert (1/30/09) J. Metcalfe (8/27/08)
DSI Inspection Clinical Pharmacology site	C.T. Viswanathan (1/9/09)
OSE/ Epidemiology	K. Gelprin (6/27/08) OSE RCM: #2008-269
OSE/Division of Medication Error Prevention Review	L. Pincock (2/6/09) Z. Oleszezuk (7/9/08)
SEALD	J. Delasko (11/13/08)

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
SEALD=Study Endpoints and Label Development Division
Note that the review material noted above relates to this current cycle. In addition, material prepared for the FDA Backgrounder for the Advisory Committee has been reviewed. I have consulted materials from cycle 1 and 2 in my prior reviews.

[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.

[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.

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/s/

Joyce Korvick
2/26/2009 09:24:47 AM
MEDICAL OFFICER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22246	ORIG-1	WILMINGTON PHARMA INC	METOZOLV ODT
NDA-22246	ORIG-1	WILMINGTON PHARMA INC	METOZOLV ODT

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/s/

JOYCE A KORVICK
09/04/2009
signatory memo