

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-246

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2) Complete Response Resubmission
Application Number(s) Priority or Standard	NDA 22-246 Standard
Submit Date(s) PDUFA Goal Date	March 11, 2009 September 11, 2009
Reviewer Name(s) Review Completion Date	Christopher Leptak, MD/PhD August 21, 2009
Established Name	metoclopramide hydrochloride orally disintegrating tablet
Trade Name	METZOLV ODT
Therapeutic Class	Prokinetic agent
Applicant	Wilmington Pharmaceuticals
Indication(s)	1. Symptomatic gastroesophageal reflux 2. Diabetic gastroparesis
Formulation	Orally Disintegrating Tablet (ODT)
Dosing Regimen	10 mg before each meal and at bedtime
Intended Population(s)	Adults

I. Synopsis

This reviewer recommends approval of NDA 22-246. The deficiencies noted from the first review cycle have been adequately addressed. The final package insert, medication guide, and REMS documents are included in Appendix 1, 2, and 3, respectively.

Since the approval of NDA 22-246 was recommended from a clinical standpoint during the original review cycle and an approval action was only contingent upon a REMS development plan as well some outstanding CMC product labeling issues, the NDA clinical review template was not used for this resubmission review.

II. Regulatory Background

Original NDA Submission

NDA 22-246 was originally submitted 29 January, 2008. A Complete Response regulatory action was taken 26 February, 2009. The primary clinical reviewer, Dr. Fathia Gibril, made the following conclusions and recommendations in her review dated 22 October, 2008:

From a clinical standpoint, the approval of metoclopramide orally disintegrating tablet (Metozolv ODT) is recommended for the following indications in adults:

- Short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy.
- Relief of symptoms associated with acute and recurrent diabetic gastroparesis for 2 to 8 weeks of therapy.

To gain approval, the sponsor needs to incorporate the NDA review team labeling recommendations as well as the addition of a BOXED WARNING and the use of appropriate risk communication plan such as Medication Guide to assure a safe use.

Complete Response Regulatory Action

In the 26 February, 2009, Complete Response letter, the following deficiencies were identified and summarized below:

1. Risk evaluation and mitigation strategy requirements (REMS)

Metoclopramide-containing products have been identified to have a significant risk of developing tardive dyskinesia (TD). NDA 22-246 must include the addition of a boxed warning and warnings section describing the potential TD risk associated with Metozolv ODT use. In addition, a medication guide (MG) and timetable for REMS component assessments must also accompany the NDA's resubmission.

2. Packaging

Specific recommendations were made to the Applicant regarding the carton and blister labeling. Resubmission of the NDA must satisfy the described concerns.

3. Product stability

Expiration dating determination requires the submission of additional CMC stability study information.

4. Safety Update

Although no new clinical trial data is required for resubmission of the NDA, please provide an updated review of the relevant literature since the original submission.

NDA Resubmission

NDA 22-246 is resubmitted for review of the actions taken to address the identified deficiencies from the original submission review cycle. No new clinical study data was required, and none was submitted.

III. Actions to address Complete Response deficiencies

1. REMS Requirements

A. Metoclopramide class-labeling action for tardive dyskinesia

Background

Metoclopramide-containing products are currently marketed as prescription drugs in both oral and injection formulations. The original approval for this class of products was for an injectable formulation of metoclopramide hydrochloride (NDA 17-862, Baxter Healthcare Corporation) and was approved by the FDA on February 7, 1979. A metoclopramide oral solution (NDA 18-821, Robins AH) was approved by FDA on March 25, 1983 but was subsequently discontinued. This drug product for NDA 18-821 was the referenced innovator product to which subsequent generic equivalent drug products were compared.

Although metoclopramide-containing products have historically been shown to cause a spectrum of movement disorders, especially with prolonged use, a study undertaken by FDA OSE epidemiologists (Kaplan et al., "Duration of therapy with metoclopramide: a prescription claims data study." *Pharmacoepi Drug Safety*, 2007, 16: 878-881), which included a review of a claims data database, demonstrated that prolonged treatment with metoclopramide (longer than 90 days cumulative use) was common.

In follow up, an OSE review dated June 27, 2008, evaluated the impact of prescribing patterns in which treatment duration extended beyond that recommended in the product labeling. That review concluded that metoclopramide use in chronic conditions such as GERD should be limited to patients for whom other safer treatment options have been exhausted, and initiated only after the patient has been informed of the risks and early warning signs of metoclopramide-induced movement disorders.

To heighten awareness of the risks of developing movement disorders that can become irreversible, especially in the setting of increased duration of exposure or increased cumulative

dose, the review recommended the addition a risk mitigation strategy including: 1) addition of a boxed warning, 2) an appropriate risk communication plan, including a medication guide and public health advisory, 3) consideration of convening an Advisory Committee, and 4) consideration of a long-term safety study to assess the risks associated with long-term metoclopramide use.

Based on this information and recommendations, companies with marketed metoclopramide-containing products were notified in December 2008 that their products had an identified safety issue that required the submission of a Risk Evaluation and Mitigation Strategy (REMS). To guide the companies, the notification included language recommendations regarding tardive dyskinesia (TD), the most common form of irreversible movement disorder associated with long-term metoclopramide use.

On 26 February, 2009, FDA sent a letter invoking its authority under section 505(o)(4) of the FDCA to require safety related label changes to address the risk of TD associated with the use of metoclopramide-containing products based on new safety information about this risk identified since the products were approved.

Since NDA 22-246 for Metozolv ODT was under active review during this safety evaluation and action, the requirements for the metoclopramide-class labeling applied to this product as well and were included in the Complete Response letter.

Proposed Package Insert Language:

1. Addition of Boxed Warning

WARNING: TARDIVE DYSKINESIA

Treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dose.

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

Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia.

See WARNINGS

2. Addition of TD discussion to the Warnings Section of the product labeling

WARNINGS:

Tardive Dyskinesia (see Boxed Warnings)

Treatment with metoclopramide can cause tardive dyskinesia (TD), a potentially irreversible and disfiguring disorder characterized by involuntary movements of the face, tongue, or extremities. Although the risk of TD with metoclopramide has not been extensively studied, one published study reported a TD prevalence of 20% among patients treated for at least 12 weeks. Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing TD.

Although the risk of developing TD in the general population may be increased among the elderly, women, and diabetics, it is not possible to predict which patients will develop metoclopramide-induced TD. Both the risk of developing TD and the likelihood that TD will become irreversible increase with duration of treatment and total cumulative dose.

Metoclopramide should be discontinued in patients who develop signs or symptoms of TD. There is no known effective treatment for established cases of TD, although in some patients, TD may remit, partially or completely, within several weeks to months after metoclopramide is withdrawn.

Metoclopramide itself may suppress, or partially suppress, the signs of TD, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of TD is unknown. Therefore, metoclopramide should not be used for the symptomatic control of TD.

Reviewer's Comment:

Based on review of the information FDA shared with the manufacturers of the metoclopramide-containing products, the review team made several modifications to the original proposal. These modifications were made after internal discussion between the review team and the internal consultants. After discussing the primary literature and the previous review team's recommendations, the new review team focused the TD discussion to highlight the main safety concern: extended duration of use and total cumulative dose beyond the label's recommendation. In addition, since the relevant literature studies could not readily differentiate sub-group risk factors associated with development of TD verses TD-associated with metoclopramide use, this information was removed from the boxed warning and discussed in greater detail in the Warning Section of the label.

B. Other Package Insert Labeling beyond the TD Discussions (see full labeling in Appendix 1)

1. Adverse Reactions (Highlights Section): Only those adverse reactions (AEs) that were identified in Metozolv ODT clinical trials are included per the PI guidelines. Other AEs that may be held in common with other metoclopramide-containing products are listed in the post-marketing experience section 6.2.
2. Pediatric Use: Although Metozolv ODT is not indicated for pediatric patients, specific reference is included in the product labeling to indicate that safe and effective use of Metozolv ODT in pediatric patients have not been established.
3. Clinical Pharmacology Recommendations (please see Clinical Pharmacology review by Dr. Kristina Estes dated June 18, 2009 for full details):
 - a. Section 2, Dosage and Administration amended to more clearly describe the tablet disintegration time and the food-effect statement.
 - b. Section 5.6, Congestive Heart Failure and Ventricular Arrhythmia amended (b) (4)
 - c. Section 8.6, Other Special Populations amended to clarify the use of Metozolv ODT in the setting of liver disease (b) (4)
4. Section 17, Patient Counseling Information. This section was expanded based on the recommendations of the SEALD reviewer.

Proposed Medication Guide

The Medication Guides for the metoclopramide class of products were harmonized with respect to the TD safety concerns and other identified class-associated topics. The full MG is included in Appendix 2.

Reviewer's Comment:

Since the MGs for the metoclopramide-containing products were harmonized, the MG for Metozolv ODT was amended to include class-specific language shared by the other metoclopramide class product MGs. For those sections unique to Metozolv ODT, the language was modified to reflect the information contained in the PI.

Proposed REMS Documents

The original submission of the REMS assessment plan was found to be unacceptable by the SEALD reviewer. The comments and recommendations were shared with the Applicant who modified the REMS documents accordingly. The final REMS documents were agreed upon by the Agency and the Applicant and are included in Appendix 3.

Reviewer's Comment:

The REMS goal was harmonized to be consistent with other metoclopramide-containing products. The assessments and timelines were found to be adequate upon input from the Agency and modifications by the Applicant.

Internal Consultants for PI and MG:**Division of Drug Marketing, Advertising, and Communications (DDMAC)****Division of Risk Management (DRISK)****Division of Medication Error Prevention and Analysis (DMEPA)****Study Endpoints and Labeling Development Team (SEALD)**

The consultant's reviews, comments, and recommendations were based on Applicant's proposed package insert (PI), medication guide (MG), and REMS materials. Upon internal discussion, the final PI, MG, and REMS documents reflect the internally agreed upon recommendations of the consultants that were ultimately accepted by the Applicant in their final form.

Recommendation for metoclopramide-class labeling REMS requirement, including TD additions to PI, the accompanying MG, and the REMS documents:

This reviewer agrees that the newly proposed labeling better reflects the risk factors associated with metoclopramide-induced TD based upon a review of the literature and following discussion with Dr. P. Jay Pasricha, the lead author of the most recently published summary of the topic (Nature Clinical Practice, March 2006, Vol. 3, No. 3, pp. 69-79). The other sections of the PI have been amended since the original submission based on the recommendations of the internal consultants. The recommendation is to approve the PI labeling, MG, and REMS documents as proposed in Appendix 1, Appendix 2, and Appendix 3, respectively.

2. Packaging and Product Stability

At the time of completion of this review, the CMC review by Dr. Maria Kowblansky was not yet completed. However, the Agency and Applicant have verbal agreements that are acceptable to both parties regarding the appropriate labeling of the product cartons and blister packaging. Additionally, the stability data is under review and the appropriate expiration dating has been agreed upon.

3. Safety Update

No clinical data was submitted or required as part of the resubmission of NDA 22-246; no clinical deficiencies were noted as part of the original review cycle.

V. Final Recommendation

This reviewer finds that the deficiencies surrounding the tardive dyskinesia safety concern from the original review cycle have been adequately addressed in the amended PI, MG, and supporting REMS documents. Additional modifications have been made to the PI labeling compared to that of the original review cycle based upon internal consultant recommendations and further discipline review.

Of note, NDA 22-246 is a 505(b)(2) application for a active drug product that is currently marketed under other trade names. The application does not seek a new indication, new dosage form, new route of administration, new dosing regimen, or new active ingredient, and therefore, was not presented before PeRC. No future post-marketing pediatric studies are required at this time.

25 Pages Withheld as b(4) Draft Labeling

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22246	ORIG 1	NO FIRM	ZYDUS
NDA 22246	ORIG 1	NO FIRM	ZYDUS
NDA 22246	ORIG 1	NO FIRM	ZYDUS
NDA 22246	ORIG 1	NO FIRM	ZYDUS
NDA 22246	ORIG 1	NO FIRM	ZYDUS
NDA 22246	ORIG 1	NO FIRM	ZYDUS

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/s/

CHRISTOPHER L LEPTAK
08/24/2009

NANCY C SNOW
08/24/2009

The acting Medical Team Leader agrees with the recommendations of the Clinical Reviewer. The Clinical Review has addressed all outstanding issues, and will serve as the CDTL memo.

CLINICAL REVIEW

Application Type NDA
Submission Number 22-246
Submission Code 000

Letter Date January 29, 2008
Stamp Date January 30, 2008
PDUFA Goal Date November 30, 2008

Reviewer Name Fathia Gibril, MD
Review Completion Date October 22, 2008

Established Name Metoclopramide
(Proposed) Trade Name Metozolv ODT
Therapeutic Class Prokinetic Agent

Applicant Wilmington Pharmaceuticals

Priority Designation S

Formulation Orally Disintegrating Tablet (ODT)

Dosing Regimen 10 mg before each meal & at bedtime
Indication Relief of Symptomatic GERD and Relief of
Symptoms Associated with Diabetic
Gastroparesis

Intended Population Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical standpoint, the approval of metoclopramide orally disintegrating tablet (Metozolv ODT) is recommended for the following indications in adults:

- Short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy.
- Relief of symptoms associated with acute and recurrent diabetic gastroparesis for 2 to 8 weeks of therapy.

To gain approval, the sponsor needs to incorporate the NDA review team labeling recommendations as well as the addition of a BOXED WARNING and the use of appropriate risk communication plan such as Medication Guide to assure a safe use.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Agency approved Reglan (metoclopramide) injectable formulation in 1979 (NDA 17-862), and Reglan tablet formulation in 1980 (NDA 17-854). Reglan oral solution was approved in 1983 (NDA 18-821), but subsequently was discontinued. Metoclopramide orally disintegrating tablet (Reglan™ RPT) was approved in 2005 (NDA 21-793), however, for financial reasons the firm decided not to market the product.

The oral formulations 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 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 reflected in the WARNING section of the Reglan tablets USPI.

However, despite the aforementioned important safety concern, and the label recommendation that therapy should not to exceed 12 weeks, a prolonged use of the product has been reported according to the OSE review dated June 27, 2008 by Dr Kate Gelperin (see her review for detail information). The OSE review noted that while the metoclopramide is used mostly for conditions

for which it is indicated (i.e., GERD and gastroparesis), drug utilization data have suggested that it is dispensed to a large population and thus may be used more liberally than recommended, given that it is only indicated as second line therapy in patients who fail to respond to conventional therapy in GERD, and the duration of use not to exceed 12 weeks. 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. Review of data from outpatient drug usage for the years from 2002 to 2007 shows that although metoclopramide is widely used in the US for GERD and gastroparesis, most of the uses were for GERD.

The OSE reviewer concluded that in light of the serious risk of irreversible drug-induced movement disorder such as TD, metoclopramide use in chronic conditions such as GERD should be limited only to patients for whom other safer treatment options have been exhausted, and initiated only after the patient has been informed of the risks and early warning signs. 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. From a regulatory and public health perspective, heightened awareness of the risk of movement disorders with metoclopramide use is urgently needed.

As a first step to call increased attention to the risk of movement disorders particularly TD, safety related changes such as addition of a BOXED WARNING in the label is recommended. An appropriate risk communication plan, including Medication Guide and Public Health Advisory is also recommended to increase awareness of early signs of irreversible as well as reversible movement disorders.

MO comments: It should be noted that metoclopramide is the only product currently approved for diabetic gastroparesis indication. There are currently many approved medical therapies such as acid suppressing agents (H₂-receptor antagonists and proton pump inhibitors) available for GERD indication, while metoclopramide is approved as a second line therapy for the indication. It is worth noting that 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. However, given the reported prolonged and frequent use of the product in GERD and a potential risk of irreversible drug-induced TD that commonly occurred with prolonged use, the MO concurs with the regulatory recommendations made by the OSE reviewer.

1.2.2 Required Phase 4 Commitments

On April 17, 2007 pre-NDA meeting, the Agency determined that the application does not trigger Pediatric Research Equity Act (See Meeting Minutes dated May 10, 2007). This is likely because a similar dosage form (Reglan™ RPT) with the same dosing regimen for same indication has been approved in June 2005 (NDA 21-793) with a postmarketing commitment for pediatric studies.

1.2.3 Other Phase 4 Requests

There are no other phase 4 requests for this NDA

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Metoclopramide is a prokinetic agent that has a complex mechanism of action. It enhances gastrointestinal motility and is an effective anti-emetic. Anti-emetic effects of metoclopramide are mainly the result of central dopamine antagonism and increased gastric motility, it also possesses a weak 5-HT₃ 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™ RPT) was approved (NDA 21-793) based on a single comparative bioequivalence study with the 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 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.

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

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

Protocol NA464 was a randomized, two-way crossover pilot BE study in 12 healthy adults to compare a single dose prototypic formulation of Metozolv ODT 10 mg vs. RLD 10 mg in fasted subjects. The formulation used is different from a to-be-marketed formulation.

Protocol 10743701 was a randomized, three-period crossover study that compared the BA of a single fed and fasted dose of 10 mg Metozolv ODT as well as a single fed dose of 10 mg RLD. A total of 30 healthy adults were enrolled.

Please see Clinical Pharmacology review by Dr Tapash Ghosh for detail information.

Efficacy

No efficacy studies were submitted with this NDA.

1.3.3 Safety

Safety was evaluated in BE single dose cross over studies. A total of 86 subjects entered three studies with Metozolv ODT; 12 subjects entered a pilot BA study; 44 subjects entered a pivotal BE study, and 30 subjects entered a BA study. The pilot BE study data are not included because it used a formulation that was different from the to-be-marketed formulation.

A total of 96 subjects were exposed to Metozolv ODT and 72 subjects were exposed to Reglan Tablets. The adverse event profile seen with Metozolv ODT was similar to that of Reglan Tablets with the exception of a decrease in blood pressure (9.4% vs. 4.2%). All of the adverse events (AEs) experienced by the subjects were considered mild. There were no serious adverse events or death reported in these clinical trials.

The most frequently reported AEs (> 4% occurrence) associated with Metozolv ODT were nausea (4.2%), decreased blood pressure (9.4%), and headache (5.2%). The most frequently reported AEs associated with Reglan Tablets were nausea (5.6%), abnormal blood count (4.2%), increased blood pressure (4.2%), decreased blood pressure (4.2%), headache (4.2%), and dizziness (4.2%). The combined data from the fasted BE study and the food-effect study did not demonstrate any differences in the AE profile for Metozolv ODT compared to Reglan Tablets with the exception of decreased blood pressure (9.4% vs 4.2%). All of the 9 subjects with decreased blood pressure in Metozolv ODT group experienced transient hypotension (systolic and/or diastolic) 2 hours \pm 30 minutes post dose in 7 subjects, before dosing and before discharge in one subject each, which resolved spontaneously in all cases. All had asymptomatic borderline hypotension with the exception of one subject who had hypotension with mild drowsiness that has resolved spontaneously. The latter subject also experienced drowsiness without hypotension during the cross over period with the use of RLD suggesting that the hypotension is not necessarily the cause of drowsiness.

1.3.4 Dosing Regimen and Administration

Gastroesophageal Reflux Disease (GERD)

For the relief of symptomatic GERD, therapy should not exceed 12 weeks in duration. Take a 10 mg to 15 mg dose of Metozolv ODT 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, metoclopramide

may be used in single doses up to 20 mg prior to the provoking situation rather than continuous treatment.

Since there is a poor correlation between symptomatic relief and healing of esophageal lesions, any therapy directed at esophageal lesions is best confirmed by endoscopic evaluation. Although experience with the effects of metoclopramide on esophageal erosions and ulcerations is limited, healing was documented in a controlled trial using four times daily therapy at 15 mg/dose. This dosing regimen should be used when lesions are present as long as it is tolerated.

Diabetic Gastroparesis (Diabetic Gastric Stasis)

For the relief of symptoms associated with diabetic gastroparesis. Take two to eight weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation. Therapy longer than 12 weeks has not been evaluated and cannot be recommended.

Take a 10 mg dose of Metozolv ODT up to four times a day at least 30 minutes before each meal and at bedtime.

Hepatic and Renal Impairment

Some patients, such as the elderly or those with impaired kidney or liver function, may be more sensitive to the therapeutic dose or the adverse effects of metoclopramide. Therefore, these patients should start therapy at a lower dose (e.g., approximately half the recommended dosage) and the dose should be titrated according to their overall clinical response and/or adverse event profile. Dialysis is not likely to be an effective method of drug removal in overdose situations.

Instructions for Use/Handling METOZOLV ODT: Since the tablet absorbs moisture rapidly, only remove each dose from the packaging just prior to taking it. Handle the tablet with dry hands and place on the tongue. In clinical trials Metozolv ODT disintegrates on the tongue in approximately one minute with a range of 10 seconds to 14 minutes (Mean \pm SD = 76.8 \pm 110.6 seconds; median = 53.5 seconds). Metozolv ODT is designed to be taken without liquid; however, the effect of taking Metozolv ODT with liquid is unknown. (b) (4)

(b) (4) If the tablet should break or crumble while handling, discard and remove a new tablet.

MO comment: The aforementioned instructions for use/handling are the revised version of the proposed label by the clinical pharmacology reviewer (Dr Ghosh).

1.3.5 Drug-Drug Interactions

The effects of metoclopramide on gastrointestinal motility can impact the absorption of other drugs. The known drug-drug interactions are listed below.

- **Anticholinergic & Narcotic Analgesic Drugs**

The effects of metoclopramide on gastrointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers.

- **Monoamine Oxidase (MAO) Inhibitors**

Metoclopramide has been shown to release catecholamines in patients with essential hypertension; it should not be used in patients taking MAO inhibitors.

- **Drug Absorption**

Absorption of drugs from the stomach may be diminished by metoclopramide (e.g., digoxin), whereas the rate and/or extent of absorption of drugs from the small bowel may be increased (e.g., acetaminophen, tetracycline, levodopa, ethanol, cyclosporine).

- **Insulin**

Because the action of metoclopramide will hasten the movement of food to the intestines and therefore the rate of absorption, insulin dosage or timing of dosage may require adjustment. Increasing movement of food to the intestines may lead to absorption of less glucose from a meal, hence less glucose in the circulation for a particular dose of administered insulin to act upon, resulting in hypoglycemia.

- **Antidepressants, Antipsychotics, & Neuroleptics**

Concomitant use of metoclopramide should be avoided in patients taking antidepressants, antipsychotics, and/or neuroleptics as they have been associated with a significant percentage of the dystonic reactions such as tardive dyskinesia or Neuroleptic Malignant Syndrome (NMS) that have occurred in association with metoclopramide.

MO comment: the sponsor revised drug-drug interaction section of the current label for metoclopramide with information from post marketing surveillance reports and published literatures.

Special Populations

- **Pregnancy**

Pregnancy Category B

Teratology studies have been performed in rats at oral doses up to 45 mg/kg/day (about 6 times the maximum recommended human dose calculated on the basis of surface area) and in rabbits at oral doses up to 45 mg/kg/day (about 12 times the maximum recommended human dose calculated on the basis of surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

- **Labor & Delivery**

The use of metoclopramide in labor and delivery has not been studied.

- **Nursing Mothers**

Metoclopramide is excreted in human milk. Caution should be exercised when metoclopramide is administered to a nursing mother. Because of the potential for serious adverse reactions from metoclopramide in nursing infants and because of the potential for tumorigenicity (including

tumor promoting potential in rats), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

- Pediatric Use

Metozolv ODT should not be used in any pediatric population. The safety and effectiveness of Metozolv ODT in pediatric patients for gastroparesis and GERD have not been established. The safety profile of Metozolv ODT in adults cannot be extrapolated to pediatric patients. Dystonias and other extrapyramidal reactions associated with metoclopramide are more common in the pediatric population than in adults. In addition, neonates have reduced levels of NADH-cytochrome b5 reductase making them more susceptible to methemoglobinemia, a possible side effect of metoclopramide use in neonates.

- Geriatric Use

Clinical studies of Metozolv ODT did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects.

The risk of developing Parkinsonian-like side effects due to metoclopramide increases with ascending dose. Geriatric patients should receive the lowest dose that is effective. If Parkinsonian-like symptoms develop in a geriatric patient, Metozolv ODT should be discontinued. The elderly may be at greater risk for tardive dyskinesia as an AE with metoclopramide. Sedation is a potential AE associated with metoclopramide use in the elderly.

Metoclopramide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. For these reasons, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range, due to the greater frequency of decreased renal function, concomitant disease, or other drug therapy in the elderly.

- Other Special Populations

Patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. In patients with G6PD deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended.

MO comments: The sponsor noted that the aforementioned language is revised from the Agency pharmacology review of non-clinical data in NDA 18-754 that was updated with results from published articles for Reglan ODT labeling.

2 Introduction and Background

2.1 Product Information

Metoclopramide is a prokinetic agent that has a complex mechanism of action. It enhances gastrointestinal motility and is an effective anti-emetic. Anti-emetic effects of metoclopramide are mainly the result of central dopamine antagonism and increased gastric motility, it also possesses a weak 5-HT₃ 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™ RPT) was approved (NDA 21-793) based on a single comparative bioequivalence study with the 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 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.

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 RLD (Reglan® tablet 5 and 10 mg). In support of the application the sponsor submitted results from two comparative BE studies and from one relative BA (food-effect) study in healthy volunteers.

The proposed indications and dosing regimen for Metozolv ODT formulation are identical to that of the RLD and include:

- Short-term (4 to 12 weeks) therapy for adults with symptomatic documented GERD who fail to respond to conventional therapy.
- Relief of symptoms associated with acute and recurrent diabetic gastric stasis in adults.

For the indication of symptomatic gastroesophageal reflux failing to respond to conventional therapy, a dose of 10 mg to 15 mg of Metozolv ODT orally up to four times a day 30 minutes before each meal and at bedtime is recommended. Therapy should not exceed 12 weeks in duration.

For the indication of relief of symptoms associated with acute and recurrent diabetic gastric stasis, a dose of 10 mg of Metozolv ODT 30 minutes before each meal and at bedtime for two to eight weeks is recommended. Therapy longer than 12 weeks has not been evaluated and cannot be recommended.

2.2 Currently Available Treatment for Indications

There are other medications approved in the United States for the treatment of GERD. The conventional therapy for GERD includes a combination of dietary and lifestyle modification, and antisecretory agents. The antisecretory agents commonly used are the H₂-receptor antagonists, including ranitidine, cimetidine, famotidine and nizatidine or proton pump inhibitors (PPIs) including omeprazole, esomeprazole, pantoprazole, lansoprazole and rabeprazole.

The most commonly used drugs in the treatment of gastroparesis are metoclopramide, Erythromycin, Cisapride, and Domperidone. However, metoclopramide is the only drug approved by the Agency for this indication.

2.3 Availability of Proposed Active Ingredient in the United States

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™ RPT) was approved (NDA 21-793) based on a single comparative BE study with Regal tablet, but has not been marketed.

2.4 Important Issues With Pharmacologically Related Products

See Section 1.2, subsection 1.2.1 of this review.

2.5 Presubmission Regulatory Activity

In March and April, 2004, the sponsor conducted a proof of concept BA study comparing the Metozolv ODT to Reglan tablet. In a Type B meeting held on November 4, 2004 it was agreed that if the PK profiles for the two formulations are the same, the Agency's previous findings of safety for Reglan may be sufficient. IND 70,578 was filed January 27, 2006 to allow for the conduct of the definitive BE study. In a pre-NDA meeting held on April 17, 2007, the Agency requested that the sponsor conduct a food effect study on Metozolv ODT. In addition, the pre-NDA background package detailed the sponsor's approach to pediatric deferral for GERD in children. However, the Agency noted that this application does not trigger PREA at this time (see Meeting Minutes dated May 10, 2007). This is likely because a similar dosage form (Reglan™ RPT) with the same dosing regimen for same indication has been approved in June 2005 (NDA 21-793) with a postmarketing commitment for pediatric studies.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

CMC review was pending at the time this review was completed.

3.2 Animal Pharmacology/Toxicology

No new animal toxicology studies were submitted in this NDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The data utilized in this review were based on the sponsor's paper submission and the electronic label submission.

4.2 Tables of Clinical Studies

Study Type	Study Identifier	Location of Study Report	Objectives	Study Design and Controls	Test Product(s), Dosage, Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	10743701	Volumes 7 – 10 Section 5.3.1.1	Comparative BA of Zydys® ODT, 10 mg in <i>fed</i> vs. <i>fasted</i> subjects - and - BA of Reglan® Tablets, 10 mg in <i>fed</i> subjects	3-way Crossover	Zydys® ODT, 10 mg Reglan® Tablets, 10 mg (oral route)	30	Healthy volunteers	Single dose	Complete; Full
BE	10643701	Volumes 11 – 13 Section 5.3.1.2	Comparative BE of Zydys® ODT, 10 mg vs. Reglan Tablet, 10 mg in <i>fasted</i> subjects	2-way Crossover	Zydys® ODT, 10 mg Reglan® Tablets, 10 mg (oral route)	44	Healthy volunteers	Single dose	Complete; Full
BE	NA464	Volumes 14 – 15 Section 5.3.1.2	Comparative BE of Zydys® ODT (prototypic formulation), 10 mg vs. Reglan Tablet, 10 mg in <i>fasted</i> subjects	2-way Crossover	Zydys® ODT, 10 mg Reglan® Tablets, 10 mg (oral route)	12	Healthy volunteers	Single dose	Complete; Full

4.3 Review Strategy

The BE and BA studies were reviewed in this 505(b)(2) submission.

4.4 Data Quality and Integrity

The application includes single dose BE studies. The NDA did not include efficacy trials. The safety data were carefully evaluated and additional information was requested on September 29, 2008 regarding the increased frequency of low blood pressure reported in subjects receiving the

test medication. The information provided by the sponsor on October 21, 2008 was found to be satisfactory and has been incorporated in the appropriate sections of this review.

4.5 Compliance with Good Clinical Practices

The sponsor states that it assured consistent execution of the protocol throughout the study, including conducting the study under the relevant ICH guidelines, commonly known as Good Clinical Practices, the applicable national requirements and the principles described in the Declaration of Helzinki as accepted by the national authority. All subjects read and signed an IRB-approved informed consent form (ICF) prior to study initiation.

4.6 Financial Disclosures

An FDA form 3454 was submitted certifying that the sponsor have not entered into any financial arrangement with the listed clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The clinical pharmacology review was pending at the time this review was completed. However, the discipline reviewer, Dr Tapash Ghosh, did not express any measure concerns during a series of NDA review team meetings held on a regular basis over the course of the NDA review.

5.2 Pharmacodynamics

Other than the BA and BE studies, Wilmington Pharmaceuticals did not conduct pharmacodynamic study.

5.3 Exposure-Response Relationships

This section is not applicable to this NDA.

6 INTEGRATED REVIEW OF EFFICACY

There were no efficacy trials submitted with this 505 (b)(2) application.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety was evaluated in BE cross-over single dose studies. A total of 86 healthy adult volunteers entered three studies; 12 subjects entered a pilot BE study; 44 subjects entered a pivotal BE study, and 30 subjects entered a food-effect study. The adverse events from the pivotal BE and food-effect study are summarized in this review. The pilot BE study data are not included because it was performed with a formulation different from a to-be-marketed formulation.

A total of 96 subjects were exposed to Metozolv ODT and 72 subjects were exposed to Reglan Tablets. A total of 33 AEs were reported in the Metozolv ODT group and 30 AEs were reported in the Reglan Tablet group. All of the events experienced by the subjects were considered mild.

7.1.1 Deaths

There were no deaths reported in the studies.

7.1.2 Other Serious Adverse Events

There were no serious adverse events reported in the studies.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Of the 44 subjects entered Study 10643701, 41 subjects completed the study and 3 subjects discontinued. The subjects who discontinued were as follows: # 25 tested positive for alcohol; # 30 dropped after check-in for the second period due to headache, nausea, and elevated blood pressure; and # 41 voluntarily withdrew for personal reasons prior to the second period.

For Study 10743701 a total of 30 subjects were entered; 28 subjects completed the first period; 27 subjects were dosed for the second period; and 25 subjects were dosed for the third period. Subjects # 4, 15, and 16 voluntarily withdrew from the study; Subject # 27 withdrew after learning of her pregnancy; and Subject # 28 withdrew due to an AE (i.e., vomiting).

A total of 12 subjects entered Study NA464; all 12 subjects completed the study.

7.1.3.2 Adverse events associated with dropouts

Of the eight subjects who discontinued the two clinical studies (three from Protocol 10643701 and five from Protocol 10743701), only two were related to an adverse event.

Subject # 30 dropped from Protocol 10643701 due to headache, nausea, and elevated blood pressure prior to dosing in the second period. Subject # 30 was a 31 years old African American female who reported a headache on April 1, 2006 at 4:30 that resolved by 7:00 pm that same day. She also reported nausea at 7:30 that same day that resolved approximately 30 minutes later. She was noted to have elevated blood pressure at 7:12 but that resolved by 7:53. The blood pressure and nausea resolved spontaneously but the headache required treatment. The severity of all events was rated mild and was concluded unrelated to study medication.

Subject # 28 discontinued Protocol 10743701 in Period III on 8/11/07 due to vomiting 89 minutes after receipt of Reglan tablet. The subject completed post-study laboratory procedures on 8/12/07, which were determined to be normal. Subject # 28 was a 21 years old African American female who was dosed at 7:13 and by 7:20 noted a mild headache that resolved by 8:30 the same day. At 8:35 she noted mild nausea, which did not resolve until 3:40 that same day. At 8:42 she vomited (severity was rated as mild). The relation of all three events noted probably related to study medication.

The MO agrees with the investigator's conclusions. The AEs reported in subjects #30 occurred prior to dosing, and are unlikely related to Metozolv, while subjects #28 experienced AEs post dosing with RLD and are likely drug related. Headache and nausea are also described as AEs in the Reglan product labeling.

7.1.3.3 Other significant adverse events

There were no other significant adverse events reported in these PK studies.

7.1.4 Other Search Strategies

There were no new or unexpected safety signals or concerns identified in the PK studies.

7.1.5 Common Adverse Events

7.1.5.1 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), which is acceptable.

7.1.5.2 Incidence of common adverse events

A total of 96 subjects were exposed to Metozolv ODT and 72 subjects were exposed to Reglan Tablets. A total of 33 AEs were reported in Metozolv ODT group and 30 AEs in Reglan Tablet group. All of the events were considered mild.

The most frequently reported AEs (> 4% occurrence) associated with Metozolv ODT were nausea (4.2%), decreased blood pressure (9.4%), and headache (5.2%). The most frequently reported AEs associated with Reglan Tablets were nausea (5.6%), abnormal blood count (4.2%), increased blood pressure (4.2%), decreased blood pressure (4.2%), headache (4.2%), and dizziness (4.2%). The combined data from the fasted BE study and the food-effect study did not demonstrate any differences in the AE profile for Metozolv ODT compared to Reglan Tablets with the exception of decreased blood pressure (9.4% vs 4.2%). All of the 9 subjects with decreased blood pressure in Metozolv ODT group experienced transient hypotension (systolic and/or diastolic) 2 hours post dose (\pm 30 minutes) in 7 subjects, before dosing and before discharge in one subject each, which resolved spontaneously in all cases. All had asymptomatic borderline hypotension with the exception of one who had hypotension with mild drowsiness that has resolved spontaneously. The latter subject also experienced drowsiness without hypotension during the cross over study with the use of RLD, suggesting that the hypotension is not necessarily the cause of drowsiness.

7.1.5.3

7.1.5.4 Common adverse event tables

Adverse Reactions in Pivotal BE and Food Effect Study in \geq 2% Subjects

Body System/Adverse Event	METOZOLV ODT N ¹ (%) ²	Reglan Tablets N ₁ (%) ²
Gastrointestinal disorders		
• Nausea	4 (4.2 %)	4 (5.6 %)
• Vomiting	2 (2.1 %)	1 (1.4 %)
General disorders and administration site conditions		
• Fatigue	2 (2.1 %)	2 (2.8 %)
Investigations		
• Full blood count abnormal	0	3 (4.2 %)
• Blood pressure increased	2 (2.1 %)	3 (4.2 %)
• Blood pressure decreased	9 (9.4 %)	3 (4.2 %)
Nervous system disorders		
• Headache	5 (5.2 %)	3 (4.2 %)
Psychiatric disorders		
• Somnolence	2 (2.1 %)	2 (2.8 %)
Vascular disorders		
• Dizziness	1 (1.0 %)	3 (4.2 %)
Number of subjects dosed with study drug	96 ³	72 ⁴

¹ N = number of subjects that reported adverse event (AE)

² Percent (%) occurrence = N divided by number of subjects dosed with respective study drug

³ Number of subjects dosed with METOZOLV ODT: Protocol 10743701 [27 under fasted conditions and 28 under fed conditions] and Protocol 10643701 [41 under fasted conditions].

⁴ Number of subjects dosed with Reglan Tablets: Protocol 10743701 [28 under fed conditions] and Protocol 10643701 [44 under fasted conditions]

Identifying common and drug-related adverse events

The investigator reports of drug-related treatment were limited to events such as headache, nausea, sedation, and abnormal blood values. Events such as sedation, nausea, and hematologic findings are also described as AEs associated with metoclopramide therapy. There were no serious, unexpected adverse events.

7.1.6 Less Common Adverse Events

A review of less common AEs did not identify any specific safety concern.

7.1.7 Laboratory Findings

There was no adverse finding during the clinical studies that was previously unreported or unassociated with the reference listed drug based on a review of the labeling.

7.1.8 Vital Signs

There were no clinically significant differences in vital signs between the two treatment groups.

7.1.9 Electrocardiograms (ECGs)

The applicant did not provide any clinical or AE data regarding ECGs in this application.

7.1.10 Immunogenicity

The applicant did not provide any clinical or AE data regarding Immunogenicity in this application. The proposed product is a chemical entity.

7.1.11 Human Carcinogenicity

The applicant did not provide any clinical or AE data regarding human carcinogenicity in this application.

7.1.12 Special Safety Studies

The NDA did not include special safety studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There were no reports of abuse with metoclopramide.

7.1.14 Human Reproduction and Pregnancy Data

No new information was provided in this 505(b)(2) application.

7.1.15 Assessment of Effect on Growth

The NDA include a single dose PK studies in adults.

7.1.16 Overdose Experience

Overdose experience is reflected in the current label.

7.1.17 Postmarketing Experience

Metozolv ODT has not been marketed in any country at the time this NDA was submitted.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Safety was evaluated in BE cross-over single dose studies. A total of 86 healthy adult volunteers entered three studies; 12 subjects entered a pilot BE study; 44 subjects entered a pivotal BE study, and 30 subjects entered a food-effect study. The pilot BE study was performed with a formulation different from a to-be-marketed formulation.

7.2.1.1 Study type and design/patient enumeration

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

Protocol 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 study was performed with a formulation different from a to-be-marketed formulation.

Protocol 10743701 was a single-dose, randomized, three-period crossover study that compared the 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. A total of 30 healthy adult subjects were enrolled.

7.2.1.3 Extent of exposure (dose/duration)

The two BE studies involved a single dose two-way and three-way cross-over design with each treatment period separated by a week washout period.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Not applicable

7.2.2.2 Postmarketing experience

Metozolv has not been marketed in any country at the time of this NDA was submitted.

7.2.2.3 Literature

The sponsor submitted paper copies of relevant published literature.

7.2.3 Adequacy of Overall Clinical Experience

The sponsor conducted BE studies in support of 505 (b)(2) application. However, the active ingredient (metoclopramide) is present in a number of marketed products for many decades.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable.

7.2.5 Adequacy of Routine Clinical Testing

The sponsor performed appropriate safety monitoring and clinical testing.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See clinical pharmacology review by Dr Tapash Ghosh.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Not applicable.

7.2.8 Assessment of Quality and Completeness of Data

From a clinical standpoint, the overall quality and completeness of the safety data are acceptable. Additional safety information was provided as per reviewer's request and was found to be satisfactory.

Please refer to CMC and clinical pharmacology reviews for their assessment and comments. These reviews were pending at the time this review was completed.

7.2.9 Additional Submissions, Including Safety Update

Not applicable.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The investigator reports of drug-related treatment were limited to events such as headache, nausea, sedation, and abnormal blood values. Even some events that were not deemed related by the investigator such as dizziness are potential side effects of metoclopramide. Other events in the current studies such as nausea and hematologic findings are also described as adverse events associated with metoclopramide therapy. There were no serious, unexpected adverse events. There are, however, limitations with the data including the short term drug exposure (single dose) and the small number of subjects studied.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

There were no significant difference in the incidence of adverse events between the individual study data and pooled data.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The studies involved single dose.

7.4.2.2 Explorations for time dependency for adverse findings

Not applicable.

7.4.2.3 Explorations for drug-drug interactions

The clinical studies did not include new drug-drug interaction studies. However, the existing drug-drug interaction section for metoclopramide label has been revised by the sponsor with information from published literature and is reflected in the proposed label.

7.4.3 Causality Determination

Not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Gastroesophageal Reflux Disease (GERD)

For the relief of symptomatic GERD, therapy should not exceed 12 weeks in duration.

Take a 10 mg to 15 mg dose of Metozolv ODT 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, metoclopramide may be used in single doses up to 20 mg prior to the provoking situation rather than continuous treatment.

Since there is a poor correlation between symptomatic relief and healing of esophageal lesions, any therapy directed at esophageal lesions is best confirmed by endoscopic evaluation. Although experience with the effects of metoclopramide on esophageal erosions and ulcerations is limited, healing was documented in a controlled trial using four times daily therapy at 15 mg/dose. This dosing regimen should be used when lesions are present as long as it is tolerated.

Diabetic Gastroparesis (Diabetic Gastric Stasis)

For the relief of symptoms associated with diabetic gastroparesis. Take 2 to 8 weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation. Therapy longer than 12 weeks has not been evaluated and cannot be recommended. Take a 10 mg dose of Metozolv ODT up to four times a day at least 30 minutes before each meal and at bedtime.

Instructions for Use/Handling METOZOLV ODT: Since the tablet absorbs moisture rapidly, only remove each dose from the packaging just prior to taking it. Handle the tablet with dry hands and place on the tongue. In clinical trials, Metozolv ODT disintegrates on the tongue in approximately one minute with a range of 10 seconds to 14 minutes (Mean \pm SD = 76.8 \pm 110.6 seconds; median = 53.5 seconds). Metozolv ODT is designed to be taken without liquid; however, the effect of taking Metozolv ODT with liquid is unknown. (b) (4)

(b) (4) If the tablet should break or crumble while handling, discard and remove a new tablet.

MO comment: The instruction for use/handling is the revised version of the proposed label by the clinical pharmacology reviewer. For detail information, please refer to his review.

8.2 Drug-Drug Interactions

The effects of metoclopramide on gastrointestinal motility can impact the absorption of other drugs. The known drug-drug interactions are listed below.

- Anticholinergic & Narcotic Analgesic Drugs

The effects of metoclopramide on gastrointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers.

- Monoamine Oxidase (MAO) Inhibitors

Metoclopramide has been shown to release catecholamines in patients with essential hypertension; it should not be used in patients taking MAO inhibitors.

- Drug Absorption

Absorption of drugs from the stomach may be diminished by metoclopramide (e.g., digoxin), whereas the rate and/or extent of absorption of drugs from the small bowel may be increased (e.g., acetaminophen, tetracycline, levodopa, ethanol, cyclosporine).

- Insulin

Because the action of metoclopramide will hasten the movement of food to the intestines and therefore the rate of absorption, insulin dosage or timing of dosage may require adjustment. Increasing movement of food to the intestines may lead to absorption of less glucose from a meal, hence less glucose in the circulation for a particular dose of administered insulin to act upon, resulting in hypoglycemia.

- Antidepressants, Antipsychotics, & Neuroleptics

Concomitant use of metoclopramide should be avoided in patients taking antidepressants, antipsychotics, and/or neuroleptics as they have been associated with a significant percentage of the dystonic reactions such as tardive dyskinesia or Neuroleptic Malignant Syndrome (NMS) that have occurred in association with metoclopramide.

MO comment: the sponsor revised drug-drug interaction section of the current label for metoclopramide with information from post marketing surveillance reports and published articles. The revised language is reflected in the proposed labeling.

8.3 Special Populations

- Pregnancy

Pregnancy Category B

Teratology studies have been performed in rats at oral doses up to 45 mg/kg/day (about 6 times the maximum recommended human dose calculated on the basis of surface area) and in rabbits at oral doses up to 45 mg/kg/day (about 12 times the maximum recommended human dose calculated on the basis of surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

- Labor & Delivery

The use of metoclopramide in labor and delivery has not been studied.

- Nursing Mothers

Metoclopramide is excreted in human milk. Caution should be exercised when metoclopramide is administered to a nursing mother. Because of the potential for serious adverse reactions from metoclopramide in nursing infants and because of the potential for tumorigenicity (including

tumor promoting potential in rats), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

- Geriatric Use

Clinical studies of Metozolv ODT did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects.

The risk of developing Parkinsonian-like side effects due to metoclopramide increases with ascending dose. Geriatric patients should receive the lowest dose that is effective. If Parkinsonian-like symptoms develop in a geriatric patient, Metozolv ODT should be discontinued. The elderly may be at greater risk for tardive dyskinesia as an adverse event with metoclopramide. Sedation is a potential adverse event associated with metoclopramide use in the elderly.

Metoclopramide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. For these reasons, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range, due to the greater frequency of decreased renal function, concomitant disease, or other drug therapy in the elderly.

- Other Special Populations

Patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. In patients with G6PD deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended.

MO comments: The sponsor noted that the aforementioned language is revised from the Agency pharmacology review of non-clinical data in NDA 18-754 that was updated with results from published articles for Reglan ODT labeling.

8.4 Pediatrics

Metozolv ODT should not be used in any pediatric population. The safety and effectiveness of Metozolv ODT in pediatric patients for gastroparesis and GERD have not been established. The safety profile of Metozolv ODT in adults cannot be extrapolated to pediatric patients. Dystonias and other extrapyramidal reactions associated with metoclopramide are more common in the pediatric population than in adults. In addition, neonates have reduced levels of NADH-cytochrome b5 reductase making them more susceptible to methemoglobinemia, a possible side effect of metoclopramide use in neonates.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

The sponsor submitted paper copies of relevant articles and the information is incorporated as deemed appropriate.

8.7 Postmarketing Risk Management Plan

Please see subsection 9.3.1 below.

8.8 Other Relevant Materials

There are no other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

In the current 505(b)(2) submission, the sponsor is seeking approval of a new metoclopramide orally disintegrating tablet (Metozolv ODT) for short term therapy (<12 weeks) of symptomatic GERD who failed to respond to conventional therapy and diabetic gastroparesis in adults. The proposed indications and dosing regimen are the same as the reference listed drug (RLD) Reglan® tablet (metoclopramide tablet). In support of the application, the sponsor submitted results from one comparative BE studies and one relative BA (food-effect) study in healthy volunteers (see clinical pharmacology review for detail information). The two comparative BE and BA studies showed that Metozolv ODT has similar safety profile to that of Reglan Tablet.

Metoclopramide, an antidopaminergic gastrointestinal prokinetic agent, is well known to cause a spectrum of movement disorders, some of which are irreversible that occur commonly during prolonged treatment with the product. The risk of developing irreversible movement disorders such as TD with prolonged use of metoclopramide has been a longstanding safety concern and has been reflected in the WARNING section of the Reglan tablets USPI. Despite this important safety concern and the current label recommendation that therapy should not to exceed 12 weeks, a prolonged and frequent use of metoclopramide particularly in GERD has been reported, according to the OSE review (see review dated June 27, 2008 for detail information).

It should be noted that metoclopramide is the only product currently approved for diabetic gastroparesis indication. There are currently many approved medical therapies such as acid suppressing agents (H₂-receptor antagonists and PPIs) available for GERD indication, while metoclopramide is approved as a second line therapy for the indication. It is worth noting that 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.

However, given the reported prolonged and frequent use of the product particularly in GERD, safety related changes such as a BOXED WARNING should be included in the labeling and an appropriate risk communication plan such as Medication Guide is also recommended to increase awareness of early signs of TD and to ensure that the benefits of the product outweigh the risk.

9.2 Recommendation on Regulatory Action

From a clinical standpoint, the approval of Metozolv ODT is recommended by the Medical Officer for the following indications in adults:

- Short-term (4 to 12 weeks) therapy for adults with symptomatic, documented GERD who fail to respond to conventional therapy.
- Relief of symptoms associated with acute and recurrent diabetic gastroparesis (gastric stasis).

To gain approval, the sponsor needs to incorporate the NDA review team labeling recommendations as well as the addition of a BOXED WARNING and the use of appropriate risk communication plan such as Medication Guide for safe use.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The Agency approved Reglan (metoclopramide) injectable formulation in 1979 (NDA 17-862), and Reglan tablet formulation in 1980 (NDA 17-854). Reglan oral solution was approved in 1983 (NDA 18-821), but subsequently was discontinued. Metoclopramide orally disintegrating tablet (Reglan™ RPT) was approved in 2005 (NDA 21-793), however, for financial reasons the firm decided not to market the product.

The oral formulations 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 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 reflected in the WARNING section of the Reglan tablets USPI.

However, despite the aforementioned important safety concern, and the label recommendation that therapy should not to exceed 12 weeks, a prolonged use of the product has been reported according to the OSE review dated June 27, 2008 by Dr Kate Gelperin (see her review for detail information). The OSE review noted that while the metoclopramide is used mostly for conditions for which it is indicated (i.e., GERD and gastroparesis), drug utilization data have suggested that it is dispensed to a large population and thus may be used more liberally than recommended, given that it is only indicated as second line therapy in patients who fail to respond to conventional therapy in GERD, and the duration of use not to exceed 12 weeks. 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. Review of data from outpatient drug usage for the years from 2002 to 2007 shows that although metoclopramide is widely used in the US for GERD and gastroparesis, most of the uses were for GERD.

The OSE reviewer concluded that in light of the serious risk of irreversible drug-induced movement disorder such as TD, metoclopramide use in chronic conditions such as GERD should be limited only to patients for whom other safer treatment options have been exhausted, and initiated only after the patient has been informed of the risks and early warning signs. 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. From a regulatory and public health perspective, heightened awareness of the risk of movement disorders with metoclopramide use is urgently needed.

As a first step to call increased attention to the risk of movement disorders particularly TD, safety related changes such as addition of a BOXED WARNING in the label is recommended. An appropriate risk communication plan, including Medication Guide and Public Health Advisory is also recommended to increase awareness of early signs of irreversible as well as reversible movement disorders.

MO comments: It should be noted that metoclopramide is the only product currently approved for diabetic gastroparesis indication. There are currently many approved medical therapies such as acid suppressing agents (H2-receptor antagonists and PPIs) available for GERD indication, while metoclopramide is approved as a second line therapy for the indication. It is worth noting that 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. However, given the reported prolonged and frequent use of the product in GERD and a potential risk of irreversible drug-induced TD that commonly occurred with prolonged use, the MO concurs with the regulatory recommendations made by the OSE.

9.3.2 Required Phase 4 Commitments

On April 17, 2007 pre-NDA meeting, the Agency determined that the application does not trigger Pediatric Research Equity Act (See Meeting Minutes dated May 10, 2007). This is likely because a similar dosage form (Reglan™ RPT) with the same dosing regimen for same

indication has been approved in June 2005 (NDA 21-793) with a postmarketing commitment for pediatric studies.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Comments to Applicant

The safety related changes described above should be communicated to the applicant.

10 APPENDICES

10.1 Labeling Review

The major labeling review includes the addition of a BOXED WARNING drafted by the DGP and OSE and specific wordings include:

(b) (4)



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/s/

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