CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-793

MEDICAL REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 6/7/2005

FROM: Joyce A Korvick, MD, MPH

DGCDP/ODE III

SUBJECT: Deputy Director Approval Comments
NDA 21-793

APPLICANT: **Schwarz Pharma**

DRUG: **Tradename™ (metaclopramide orally disintegrating tablet)**

DIVISION RECOMMENDATION:
The division recommends the approval of Tradename™ (metaclopramide orally disintegrating tablets) for the following indications:

- 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 gastric stasis.

I concur with this recommendation.

For the indication of symptomatic gastroesophageal reflux failing to respond to conventional therapy, a dose of 10 mg to 15 mg of metaclopramide orally disintegrating tablets orally up to four times a day, 30 minutes before each meal and at bedtime is recommended.
For the indication of relief of symptoms associated with acute and recurrent diabetic gastric stasis, a dose 10 mg of metaclopramide orally disintegrating tablets 30 minutes before each meal and at bedtime for two to eight weeks is recommended.

I. Regulatory History:

On December 27, 2001 A.H. Robins Company transferred NDA 17-854 (Reglan® tablets) to Schwartz Pharma Inc (SPInc.) and at the same time, withdrew NDA 18-821 (Reglan® syrup). On December 31, 2002 NDA 17-862 for Reglan® Injection was transferred from A.H. Robins Company to Baxter Healthcare Corporation.
On November 8, 2002, a pre-NDA meeting was held between the agency and the sponsor, SPInc., to discuss the proposed new dosage form of orally disintegrating tablets.

The sponsor cross-referenced the efficacy and safety data contained in NDA 17-854 in support of a 505(b)(1) application for the new dosage form. It was agreed that if the pharmacokinetic (PK) profiles for the two formulations (i.e., 10 mg

Reglan Tablet and the 10 mg orally disintegrating tablet) were the same, the preclinical studies for the original NDA may be sufficient to support the new formulation and the original clinical studies could support the new formulation.

In this 505(b)(1) submission, the sponsor the sponsor conducted bioequivalence study SP759, an open-label, randomized, 3-way crossover, single center trial comparing metoclopramide 10 mg orally disintegrating tablet with and without water vs. metoclopramide 10 mg tablet with water. A total of 21 subjects were enrolled and 20 subjects completed the study.

A biowaiver request for the food effect and for the lower strength 5 mg metaclopramide orally disintegrating tablets was also requested by the sponsor.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

Chemistry and Manufacturing:

No major chemistry issues were identified. Given the fact that this tablet is very friable it was felt that scoring the tablet would not reliably deliver the expected dose. The division recommended that the sponsor remove the scoring. The sponsor agreed.

Clinical Pharmacology:

The sponsor demonstrated bioequivalence of the 10 mg Reglan tablet to 10 mg metaclopramide orally disintegrating tablets in bioequivalence study SP759. The requested biowaiver can be granted for the lower strength, 5 mg ODT, since both 5 and 10 mg strengths of metaclopramide orally disintegrating tablets are compositionally proportional and show similar dissolution characteristics.

The proposed dosing regimen for metaclopramide orally disintegrating tablets is the same as the Reglan IR tablets for the same clinical indications. The biowaiver request for the food effect study can be granted according to the reviewers.

An important issue for labeling is the expression of the amount of time it would take for the tablet to dissolve in the mouth. This was discussed with the sponsor and an average time range was agreed upon and placed in the final label.

Pharmacology/Toxicology:

No new animal or toxicology studies were submitted in this NDA. It was agreed that if the product was bioequivalent to the approved product then none would be required. However, the sponsor submitted published reports of additional genotoxicity testing and study of metaclopramide tumor promoting potential in rats. These positive findings are discussed in the labeling under Precautions; carcinogenesis, Mutagenesis, Impairment of Fertility; Pregnancy; Nursing Mothers. The labeling recommendations, which correct the primary pharmacology toxicology review, can be seen in Dr. Choudary's supervisory pharmacology/toxicology review.

III. **Pediatric Use:** This is deferred for pediatric patients birth to 16 years. Currently the Pediatrics Division is writing a WR for this drug because of its off label use.

IV. **Labeling Recommendations:**
Trade Name: The sponsor proposed the name Reglan [redacted] in the original submission. The division reviewers recommended against this use of this name as it may be promotional and infer rapid dissolution. In some patients it can take up to 4 minutes to dissolve. The sponsor has submitted new trade names which are currently under review. It was decided that the label would be approved with out a specific trade name at this point. This would be remedied by a supplemental application.

V. **Phase IV Commitments:** These are related to the PREA deferral. We are recommending the following studies and the sponsor has agreed with the caveat that they will need to discuss this further after the WR is published. The PK studies that we are interested in are listed in the approval letter.

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/s/

Joyce Korvick
6/10/05 02:06:31 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-793
Letter Date	7-30-04
Stamp Date	8-4-04
PDUFA Goal Date	6-10-05
Reviewer Name	Lolita A. Lopez, M.D.
Review Completion Date	May 9, 2005
Established Name	Mecloclopramide Orally Disintegrating Tablets
(Proposed) Trade Name	Reglan [redacted]
Therapeutic Class	Prokinetic
Applicant	Schwarz Pharma
Priority Designation	Standard
Formulation	Orally Disintegrating Tablet
Dosing Regimen	10 mg tablet before each meal
Indication	Relief of Symptomatic GER Relief of Symptoms Associated with Diabetic Gastroparesis
Intended Population	Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The approval of metoclopramide orally disintegrating tablet (Reglan [redacted]') is recommended by this Medical Officer for the following indications:

- 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 gastric stasis.

For the indication of symptomatic gastroesophageal reflux failing to respond to conventional therapy, a dose of 10 mg to 15 mg of Reglan [redacted]' orally up to four times a day, 30 minutes before each meal and at bedtime is recommended.

For the indication of relief of symptoms associated with acute and recurrent diabetic gastric stasis, a dose 10 mg of Reglan [redacted]' 30 minutes before each meal and at bedtime for two to eight weeks is recommended.

To get approval, the sponsor should incorporate the labeling recommendations listed in the Medical Officer's Labeling Review (see Appendix) and the NDA Team's labeling recommendations.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management steps are recommended.

1.2.2 Required Phase 4 Commitments

Metoclopramide has applicability to the pediatric population and it represents a meaningful therapeutic benefit especially in patients with gastroesophageal reflux disease (GERD) and diabetic gastroparesis. This Medical Officer recommends that the sponsor conduct efficacy and safety study that will supply information on the benefit of this drug in patients less than one year old and older than one year old. A PK/PD study to determine the appropriate dose in these populations is recommended prior to initiating the clinical study.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests for this sNDA.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Metoclopramide (Reglan®) is a prokinetic agent that has a complex mechanism of action. It enhances gastrointestinal motility and is an effective antinauseant. Antiemetic effects of metoclopramide are mainly the result of central dopamine antagonism and increased gastric motility, it also possesses weak 5-HT_3 receptor antagonism.

A 5-mg and 10-mg tablets are currently available; a Reglan liquid product was approved but is no longer being marketed. The oral form is indicated for the short-term (4-12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux disease (GERD) who fail to respond to conventional therapy and for the relief of symptoms associated with acute and recurrent diabetic gastroparesis. The parenteral form 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.

Reglan® injection was originally approved by the FDA in 1979 and the tablet formulation was approved in 1980. On December 27, 2001 A.H. Robins Company transferred NDA 17-854 (Reglan® tablets) to Schwartz Pharma Inc (SPInc.) and at the same time, withdrew NDA 18-821 (Reglan® syrup). On December 31, 2002 NDA 17-862 for Reglan® Injection was transferred from A.H. Robins Company to Baxter Healthcare Corporation.

On November 8, 2002, a pre-NDA meeting was held between the agency and the sponsor, SPInc., to discuss the proposed new dosage form of orally disintegrating tablets. The sponsor plans to cross-reference the efficacy and safety data contained in NDA 17-854 in support of a 505(b)(1) application for the new dosage form. It was agreed upon that if the pharmacokinetic (PK) profiles for the two formulations (i.e., 10 mg Reglan Tablet and the 10 mg orally disintegrating tablet) are the same, the preclinical studies for the original NDA may be sufficient to support the new formulation and the original clinical studies could support the new formulation.

In this 505(b)(1) submission, the sponsor is seeking for the approval of a new metoclopramide orally disintegrating tablet (ODT) formulation, Reglan [redacted] 5 and 10 mg. The indications and dosing regimen proposed are be the same as the reference listed drug (RLD) Reglan® tablet 5 and 10 mg. To gain approval, the sponsor conducted

bioequivalence study SP759, an open-label, randomized, 3-way crossover, single center trial comparing metoclopramide 10 mg orally disintegrating tablet (Reglan™ [redacted]) with and without water vs. metoclopramide 10 mg tablet (Reglan® tablet) with water. A total of 21 subjects were enrolled and 20 subjects completed the study. In addition, a biowaiver request for the food effect and for the lower strength 5 mg Reglan [redacted] were also requested by the sponsor.

1.3.2 Efficacy

No efficacy studies were submitted with this NDA.

The sponsor conducted a bioequivalence study, SP759, an open-label, randomized, 3-way crossover, single center trial comparing the orally disintegrating tablet formulation, Reglan 10 mg [redacted] with and without water vs. Reglan 10 mg tablet with water (RLD). A total of 21 subjects enrolled in the study and 20 subjects completed the study. The results of the study has shown that Reglan™ [redacted] 10 mg is bioequivalent to the currently marketed Reglan® 10 mg tablet under fasting conditions; therefore, the efficacy of this new orally disintegrating formulation is expected to be similar to Reglan tablet.

1.3.3 Safety

Safety was evaluated in one clinical trial with Reglan™ [redacted]. Study SP759 was a trial performed in 21 healthy volunteers to evaluate the bioequivalence of a single dose of Reglan™ [redacted] 10 mg administered with or without water compared to a single dose of Reglan® tablets 10 mg. The sponsor assessed safety by monitoring adverse events (AEs) and serious adverse events (SAEs) at study completion or early termination. Laboratory evaluations (hematology, serum chemistry, urinalysis vital signs, and a 12-lead electrocardiogram were performed during the screening period and at study completion or early termination.

In this bioequivalence trial, 20 subjects were exposed to two doses of Reglan [redacted] 10 mg and 21 subjects were exposed to one dose of Reglan 10 mg tablets. One subject did not complete the trial, dropping out after receiving the first period medication, a Reglan 10 mg tablet. Twenty five percent (25%, 5/20) of subjects in the Reglan [redacted] treatment group experienced 13 AEs and 28.6% (6/21) of subjects in the Reglan tablet group experienced 18 AEs. The most frequent AE reported with Reglan [redacted] was oral mucosal petechiae (15%, 3/20) and with Reglan tablets were oral mucosal petechiae (9.5%, 2/21) and decreased hemoglobin (9.5%, 2/21). These were considered by the investigator to be not related to metoclopramide. Most of these AEs were classified as mild (Reglan [redacted] 84.6%; Reglan tabs 77.8%) and none were severe in intensity. No deaths were reported in this trial.

The safety profile of Reglan [redacted] is not expected to be different when compared to the safety profile of the already marketed Reglan tablets.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen and indications below for Reglan [redacted]™ 10 mg is similar to the current dosing regimen of the reference listed drug (RLD), Reglan® Tablet 10 mg. The safety and efficacy of these doses have been well-established.

For the Relief of Symptomatic Gastroesophageal Reflux
Administer from 10 mg to 15 mg of Reglan [redacted]™ orally up to q.i.d. 30 minutes before each meal and at bedtime, depending upon symptoms being treated and clinical response. If symptoms occur only intermittently or at specific times of the day, use of metoclopramide in single doses up to 20 mg prior to the provoking situation may be preferred rather than continuous treatment. Occasionally, patients (such as elderly patients) who are more sensitive to the therapeutic or adverse effects of metoclopramide will require only 5 mg per dose.

For the Relief of Symptoms Associated with Diabetic Gastroparesis (Diabetic Gastric Stasis)
Administer 10 mg of Reglan [redacted]™ 30 minutes before each meal and at bedtime for two to eight weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation.

The sponsor also included instructions for use/handling of Reglan [redacted] in the label. It states:
"Just prior to administration, remove the REGLAN [redacted]™ tablet from the bottle. Immediately place the tablet on top of the tongue where it will dissolve in seconds, then swallow with saliva. Administration with liquid is not necessary."

The dosing regimen proposed by the sponsor is acceptable as it is similar to the existing dosing regimen of the RLD. However, study SP759 have shown that Reglan [redacted] 10mg disintegrates between 38 seconds and 233 seconds (3.8 minutes), with a median disintegration time of 63 seconds, and a mean of 81.43 seconds. Therefore, the claim that this drug "dissolve in seconds" maybe a misinformation to patients in whom Reglan [redacted] takes more than a minute to dissolve. Patients should be informed of the range of time it may take for this product to dissolve or disintegrate. This information should be communicated in the package insert. Patients should be informed that this formulation typically disintegrates in less that 2 minutes.

1.3.5 Drug-Drug Interactions

The label of metoclopramide states that 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.

The finding that metoclopramide releases catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

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

Gastroparesis (gastric stasis) may be responsible for poor diabetic control in some patients. Exogenously administered insulin may begin to act before food has left the stomach and lead to hypoglycemia. Because the action of metoclopramide will influence the delivery of food to the intestines and thus the rate of absorption, insulin dosage or timing of dosage may require adjustment.

1.3.6 Special Populations

Metoclopramide is excreted in human milk; therefore, caution should be exercised when this drug is administered to a nursing mother.

In neonates, prolonged clearance may produce excessive serum concentrations. Neonates also have reduced levels of NADH-cytochrome b_5 reductase which, in combination with the aforementioned pharmacokinetic factors, make neonates more susceptible to methemoglobinemia.

Patients with NADH-cytochrome b_5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered.

The elderly may be at greater risk for tardive dyskinesia. Geriatric patients should receive the lowest dose of metoclopramide that is effective. Clinical studies of metoclopramide 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 increases with ascending dose. If parkinsonian-like symptoms develop in a geriatric patient receiving metoclopramide, this drug should generally be discontinued before initiating any specific anti-parkinsonian agents. Sedation has been reported in metoclopramide users. Sedation may cause confusion and manifest as over-sedation in the elderly.

Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40 mL/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

Safety and effectiveness in pediatric patients have not been established. The safety profile of metoclopramide 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.

The above information in special population is already reflected in the current prescribing information for metoclopramide.

Appears This Way
On Original

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Metoclopramide (Reglan®) is a prokinetic agent, and a derivative of para-aminobenzoic acid structurally related to procainamide. Its effects are confined largely to the upper digestive tract, where it increases lower esophageal sphincter tone and stimulates antral and small intestinal contractions. It belongs to a class of drugs that facilitate ACh release from enteric neurons, which may be mediated indirectly by several different mechanisms, including suppression of inhibitory interneurons by antagonism of 5-HT_3 receptors at high doses and stimulation of excitatory neurons via activation of 5-HT_4 receptors. It has both central (which is responsible for its antinauseant and antiemetic effects), and peripheral antidopaminergic effects (which contributes to its prokinetic activity).

Reglan® injection was originally approved by the FDA in 1979; the tablet form was approved in 1980. A 5-mg and 10-mg tablets are currently available; a liquid product was approved but is no longer being marketed. The oral form is indicated for the short-term (4-12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux disease (GERD) who fail to respond to conventional therapy and for the relief of symptoms associated with acute and recurrent diabetic gastroparesis. The parenteral form 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.

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 H_2-receptor antagonists such as ranitidine, cimetidine, famotidine and nizatidine or proto-pump inhibitors (PPIs) omeprazole, esomeprazole, pantoprazole, lanzoprazole and rabeprazole. An alternative for patients who require long-term, high-dose PPIs is antireflux surgery, in which the gastric fundus is wrapped around the esophagus (fundoplication) increases the lower esophageal sphincter pressure.

The most commonly used drugs in the treatment of gastroparesis are metoclopramide, erythromycin, cisaparide and dromperidone; however, metoclopramide is the only drug approved by the FDA for this indication.

2.3 Availability of Proposed Active Ingredients in the United States

Metoclopramide was originally approved by the FDA in 1979. Metoclopramide (Reglan®) tablet was approved on December 30, 1980. Metoclopramide was originally developed to treat nausea during pregnancy but is also extremely useful in the treatment of chemotherapy-induced nausea and vomiting. This medication is currently available as an oral (5 and 10 mg tablet) and parenteral form. A liquid product was approved but is no longer being marketed. The oral form is indicated for the short-term (4-12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux disease (GERD) who fail to respond to conventional therapy and for the relief of symptoms associated with acute and recurrent diabetic gastroparesis. The parenteral form 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.

2.4 Important Issues with Pharmacologically Related Drugs

The mechanism of action of metoclopramide is complex. It is a central and peripheral dopamine receptor antagonist, a serotonin 5-HT_4 agonist, a 5-HT_3 antagonist (at high doses), and a cholinesterase inhibitor. Due to its central nervous system actions, use of this drug is associated with extrapyramidal side effects (EPS) such as acute dystonic reactions, Parkinsonian-like symptoms tardive dyskenesia; drowsiness, depression, hyperprolactenemia, and neuroleptic malignant syndrome. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers.

Another prokinetic agent, cisapride, promotes gastric emptying by acting as a partial 5-HT_4 agonist that causes release of acetylcholine from the myenteric plexus. It also has a weak 5-HT_3 antagonist effect but no direct dopamine activity. However, cisapride was withdrawn from the market due to reported cases of cardiac arrhythmias associated with its use and it is only available through a limited access program.

2.5 Pre-Submission Regulatory Activity

Reglan® tablets was approved on December 30, 1980. Ownership of NDA 17-854 was transferred to Schwarz Pharma Inc. (SPInc) on December 27, 2001. Reglan® tablets (NDA 17-854) is indicated as short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy. On November 8, 2002, a pre-NDA meeting was held between the agency and the sponsor to discuss the proposed new dosage form of orally disintegrating tablets. The sponsor, SPInc. plans to cross-reference the efficacy and safety data contained in NDA 17-854 in support of a 505(b)(2) application for the new dosage form. It was agreed upon that if the pharmacokinetic (PK) profiles for the two formulations (i.e., 10 mg Reglan

tablet and the 10 mg orally disintegrating tablet) are the same, the preclinical studies for the original NDA may be sufficient to support the new formulation and the original clinical studies could support the new formulation. For details, see meeting minutes dated November 8, 2002, NDA 17-854.

2.6 Other Relevant Background Information

The efficacy of metoclopramide 5 and 10 mg tablet for the approved indications of symptomatic GER and diabetic gastroparesis have been demonstrated in NDA 17-854 and through more than 20 years of marketing experience. Its safety has been well demonstrated and well-documented as well. The extrapyramidal side effects (EPS) of metoclopramide such as acute dystonic reactions, Parkinsonian-like symptoms and tardive dyskenesia, and neuroleptic malignant syndrome are well-known to practitioners and are documented in the 'Warning' section of the label.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

See Dr. Zhengfang Ge's Chemistry Review. There are no microbiology information submitted in this review.

The orally disintegrating tablet proposed is scored, this will be a clinical concern in that patients might be encouraged to break or split the tablet in order to deliver a half dose. This will be a risk for inaccurate dosaging. Therefore, this Medical Officer highly recommends removing the scoring of this ODT formulation.

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

Table 1: Clinical Study

Type of Trial	*Objective*	*Design*	*Dosage and Administration*	*Patients*	*Duration of Treatment*
PK SP 759	**To assess bioequivalence of metoclopramide 10 mg ODT & 10 mg tablet**	**Open-label, randomized, 3-way crossover, single center, phase 1**	**Single dose of 10 mg ODT vs. 10mg tablet in fasted state, 1 week washout period**	**21 healthy subjects**	**30 hours**

4.3 Review Strategy

A pharmacokinetics trial (SP 759) was reviewed in this 505(b)(1) submission.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was consulted for this NDA and based on the evaluation of their inspectional findings, they recommend that the following data be excluded from the bioequivalence determination: Subject 16 periods 1 and 2 (item 1); Samples S12P230hr (subject, period, time), S12P30.75hr, and S12P38hr (item 2). In addition, for subjects 7 and 8, data from Run 11 and not Run 4 should be used for BE determination (item 3).

As recommended by DSI, reanalysis were performed by the Office of Biopharmaceutics. The results of reanalysis still meet the Agency's Bioequivalenc acceptance criteria. See Bipharm Review of Dr. Tien-Mien Chen.

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

Metoclopramide is rapidly and well absorbed from the gastrointestinal tract in the absence of gastroparesis. Peak plasma levels are generally achieved within 2 hours after oral dosing. Bioavailability is approximately 80% plus or minus 15.5%. Its onset of action is 1-3 minutes after intravenous administration, 10-15 minutes after intramuscular injection, and 30-60 minutes after oral dosing. It is weakly bound to plasma protein (about 30%) and is distributed into breast milk, crosses the blood-brain barrier and the placenta.

Metoclopramide appears to undergo minimal metabolism but is conjugated with sulphuric acid or glucuronic acid. It is unknown if the major metabolite 2-[(4-amino-5-chloro-2-methoxybenzoyl) amino] acetic acid has any activity. Plasma concentrations decline in a biphasic manner, with a half-life of about 5 minutes in the initial phase and 2.5-6 hours in the terminal phase. Within 72 hours, about 85% of an oral dose is excreted in the urine as unchanged drug (20%) or as the glucuronide or sulfate in patients with normal renal function. About 5% of an oral dose is excreted in the feces via the bile. The elimination and half-life of metoclopramide is prolonged in patients with renal insufficiency, and pharmacokinetic changes are linear with declining renal function.[1]

The sponsor conducted bioequivalence study SP759, an open-label, randomized, 3-way crossover, single center trial comparing Reglan 10 mg orally disintegrating tablet with and without water vs. Reglan 10 mg tablet with water (RLD). A total of 21 subjects enrolled in the study and 20 subjects completed the study. The results of the study has shown that Reglan™ [redacted] 10 mg is bioequivalent to the currently marketed Reglan®10 mg tablet under fasting conditions. (See table below.) Further, the in vitro dissolution comparisons also showed comparable dissolution data and profiles between Reglan ™ [redacted] 10 mg and Reglan® tablet 10 mg; and between Reglan 5 mg and 10 mg [redacted] Biowaiver for the lower strength of Reglan 5 mg [redacted] was recommended to be granted by Biopharmaceutics Reviewer Dr. Tien-Mien Chen, Ph.D. See Dr. Chen's Biopharmaceutics review of this NDA for details.

1 Clinical Pharmacology Online

Table 2: Results of BE Assessment for Treatment B (Test of interest) vs. Treatment C (Reference) Reported[2]

NDA 21-793 for Reglan™ (Metoclopramide ODT) BE Assessment					
PK Parameters Mean (SD)	**Treatment A**	**Treatment B (Test of interest)**	**Treatment C (Reference)**	**B vs. C Point Estimate**	**90% CI**
C_{max} (ng/ml)[1]	38.7 (14.1)	39.2 (13.9)	41.1 (14.3)	-----	-----
T_{max} (hr)[1]	1.65 (0.58)	1.88 (0.71)	1.65 (0.54)	-----	-----
$T_{1/2}$ (hr)	6.94 (1.68)	7.39 (1.91)	7.05 (1.26)	-----	-----
$AUC_{0\text{-last}}$[1] (ng-hr/ml)	357 (147)	374 (167)	368 (136)	-----	-----
$AUC_{0\text{-}\infty}$[1] (ng-hr/ml)	384 (179)	407 (208)	392 (154)	-----	-----
Ln $(C_{max})^2$	3.60 (0.344)	3.61 (0.35)	3.67 (0.32)	94.9	88.7-101.6
Ln $(AUC_{0\text{-last}})^2$	5.81 (0.375)	5.85 (0.40)	5.84 (0.37)	100.5	96.2-104.9
Ln $(AUC_{0\text{-}\infty})^2$	5.87 (0.399)	5.91 (0.43)	5.90 (0.38)	101.6	97.1-106.3

1 Arithmetic mean (± standard deviation, SD).
2 Log-transformed geometric least square mean (± SD).
Treatment A = 1 X 10 mg metoclopramide [redacted] With Water: Test
Treatment B = 1 X 10 mg metoclopramide [redacted] Without Water: Test
Treatment C = 1 X 10 mg metoclopramide **Tablet** With Water: Reference

5.2 Pharmacodynamics

Metoclopramide is a benzamide that has both central antiemetic and prokinetic effects. As reflected in the label, it stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the action of acetylcholine. Metoclopramide 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. It has little, if any, effect on the motility of the colon or gallbladder.

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.

Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions. 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 From Dr. Chen's Biopharmaceutics Review

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 NDA.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety was evaluated in one clinical trial with metoclopramide ODT. Study SP759 was a trial performed in 21 healthy volunteers to evaluate the bioequivalence of a single dose of metoclopramide 10 mg ODT administered with or without water compared to a single dose of metoclopramide 10 mg tablet (Reglan® tablet). The sponsor assessed safety by monitoring adverse events (AEs) and serious adverse events (SAEs) at study completion or early termination. Laboratory evaluations (hematology, serum chemistry, urinalysis), physical examination, vital signs, and a 12-lead electrocardiogram were performed during the screening period and at study completion or early termination.

In this bioequivalence trial, 20 subjects were exposed to two doses of Reglan™ [redacted] 10 mg and 21 subjects were exposed to one dose of Reglan® 10 mg tablets. One subject did not complete the trial, dropping out after receiving the first period medication, a Reglan 10 mg tablet. Twenty five percent (25%, 5/20) of subjects in the Reglan [redacted] treatment group experienced 13 AEs and 28.6% (6/21) of subjects in the Reglan Tablet group experienced 18 AEs. The most frequent AE reported with Reglan [redacted] was oral mucosal petechiae (3/20; 15%) and with Reglan Tablets were also oral mucosal petechiae (2/21; 9.5%) and decreased hemoglobin (2/21; 9.5%). (See table 3 below). These were considered by the investigator to be not related to metoclopramide; the remaining AEs with Reglan [redacted] were all single events. Most of these AEs were classified as mild (Reglan [redacted] 84.6%; Reglan tabs, 77.8%) and none were severe in intensity.

Table 3: All Adverse Events

System Organ Class Adverse Event	Reglan [redacted] 10 mg (N = 20) n (%)	Reglan 10 mg Tablets (N = 21) n (%)
Subjects with at least one AE	**5 (25%)**	**6 (28.6%)**
Cardiac Disorders		
Tachycardia NOS	1 (5)	0
Gastrointestinal Disorders		
Oral mucosal petechiae	3 (15)	2 (9.5)
Vomiting NOS	1 (5)	1 (4.8)
Aphthous stomatitis	0	1 (4.8)
Flatulence	0	1 (4.8)
Nausea	0	1 (4.8)
General Disorders & Administration Site Conditions		
Pain NOS	1 (5)	0
Pyrexia	1 (5)	0
Feeling hot and cold	0	1 (4.8)
Investigations		
Lymphocyte count decreased	1 (5)	0
Lymphocyte percentage decreased	1 (5)	0
Hemoglobin decreased	0	2 (9.5)
Blood urine	1 (5)	0
Urobilin urine present	1 (5)	0
Bacteria NOS urine identified	0	1 (4.8)
Nitrite urine present	0	1 (4.8)
White blood cells urine positive	0	1 (4.8)
Neutrophil count increased	0	1 (4.8)
Neutrophil percentage increased	0	1 (4.8)
Nervous System Disorders		
Headache	0	1 (4.8)
Reproductive System And Breast Disorders		
Dysmenorrhea	1 (5)	0
Respiratory Thoracic and Mediastinal Disorders		
Pharyngolaryngeal pain	1 (5)	0
Vascular Disorders		
Pallor	0	1 (4.8)

Sponsor's table Vol.12 p.221

It appears that the safety of Reglan [redacted] is not expected to be different when compared to the safety profile of the already marketed Reglan tablets. It is to be noted that the number of patients in this trial is small (N=21). However, since the active ingredient for the two formulations is the same, it will be reasonable to assume that the safety profile between the ODT and the tablet formulation will be similar.

7.1.1 Deaths

There were no deaths reported with this trial.

7.1.2 Other Serious Adverse Events

There were no serious adverse events reported in this trial.

7.1.3 Dropouts and Other Significant Adverse Events

One subject, a 21-year old female, did not complete the trial. She dropped out from the study due to an adverse event (nausea, pallor, vomiting, and feeling of hot and cold) after receiving the first period medication, a Reglan 10 mg tablet. She vomited four times the night before Period 2 dosing (a week after the first dose). The vomiting is not considered to be related to metoclopramide.

7.1.4 Other Search Strategies

There were no new safety signals or concerns identified with this PK study. It is to be noted that this trial studied only a total of 21 healthy patients.

7.1.5 Common Adverse Events

The most frequent adverse event reported in this trial were oral mucosal petechiae (Reglan [redacted] · 15%, 3/21; and Reglan tablets: 9.5%, 2/21) and decreased hemoglobin (Reglan [redacted] group: 2/21, 9.5%). See table below.

Table 4: Most Common Adverse Events

Adverse Event	Reglan [redacted] 10 mg (N=20)	Reglan Tabs 10 mg N=21)
Oral mucosal petechiae	3 (15)	2 (9.5)
Hemoglobin decreased	0	2 (9.5)

The petechiae were classified as mild in intensity and are described by the investigator as small red dots at the line where the teeth meet. The subjects were described as "cheek suckers." These AEs were considered as not related to metoclopramide (Reglan). The remaining AEs with Reglan [redacted] were all single events.

The following table illustrates treatment-related adverse events.

Table 5: Treatment–Related Adverse Events

Adverse Event	Reglan [redacted] 10 mg (N=20)	Reglan Tabs 10 mg N=21)
Pain NOS (Body aches)	1 (5)	0
Headache	0	1 (4.8)

In addition, this study has shown that the safety risk is not different when Reglan™ [redacted] is taken with or without water following disintegration on the tongue.

7.1.6 Less Common Adverse Events

The number of patients in this study is not adequate to detect or evaluate less common adverse events.

7.1.7 Laboratory Findings

There were no reported significant differences in laboratory findings between the Reglan [redacted] and tablet formulations in this trial. All laboratory AEs of either Reglan formulation were mild in intensity and unlikely treatment-related. There were no additional analyses and explorations or special assessments conducted with this NDA.

7.1.8 Vital Signs

Vital signs were performed during the screening period and at study completion or early termination. One patient in the Reglan [redacted] group experienced tachycardia, pulse rate of 115/min and was accompanied by fever (100.8°F), body aches and sore throat. The patient remained in the study. There were no significant differences in the vital signs of patients taking either formulation.

7.1.9 Electrocardiograms (ECGs)

Vital signs were performed during the screening period and at study completion or early termination. No treatment-emergent clinically significant changes in ECG were observed.

7.1.10 Immunogenicity

No data was provided regarding immunogenicity.

7.1.11 Human Carcinogenicity

An Ames mutagenicity test performed on metoclopramide was negative.

Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, an important factor to consider when prescribing metoclopramide in patients with previously detected breast cancer. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; at this time, the available evidence is too limited to be conclude. This is reflected in the current label.

7.1.12 Special Safety Studies

There are no special safety studies done in this sNDA.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no available reports of withdrawal phenomena or abuse potential at this time.

7.1.14 Human Reproduction and Pregnancy Data

Metoclopramide is listed as Pregnancy Category B. The current prescribing information states that reproduction studies performed in rats, mice and rabbits by the I.V., I.M., S.C., and oral routes at maximum levels ranging from 12 to 250 times the human dose have demonstrated no impairment of fertility or significant harm to the fetus due to metoclopramide. However, no adequate and well-controlled studies in pregnant women have been performed. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

7.1.15 Assessment of Effect on Growth

This NDA did not specifically assess the effect of metoclopramide on growth. With the 25 years experience of metoclopramide use, it is unlikely that a previously undetected rare event will now be found to occur with this new orally disintegrating formulation.

7.1.16 Overdose Experience

Overdose experience is reflected in the current label of metoclopramide. Overdosage symptoms include drowsiness, disorientation and extrapyramidal reactions. Symptoms are self-limiting and usually disappear within 24 hours. Anticholinergic or antiparkinson drugs or antihistamines with anticholinergic properties may be helpful in controlling these extrapyramidal reactions.

Hemodialysis and continuous ambulatory peritoneal dialysis removes relatively little metoclopramide. Dialysis is not likely to be an effective method of drug removal in overdose situations. Unintentional overdose reported in infants and children receiving

oral solution include seizures, extrapyramidal reactions, and lethargy. Methemoglobinemia has been reported in premature and full-term neonates who were given overdoses of metoclopramide (1 to 4 mg/kg/day orally, intramuscularly or intravenously for 1 to 3 or more days). Methemoglobinemia can be reversed by the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal.

7.1.17 Postmarketing Experience

The post-marketing safety experience of Reglan as reported to Schwarz Pharma, Inc. since December 2001 consists mainly of labeled adverse events, reflected in the prescribing information of Reglan.

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

7.2.1.1 Study type and design/patient enumeration

This trial is a three-treatment randomized, crossover design, with all subjects receiving metoclopramide as an ODT administered with or without water or as a tablet, with each treatment separated by a one week washout period.

7.2.1.2 Demographics

A total of 21 healthy subjects were enrolled in this trial, 57% were females and 43% were males. The racial distribution is as follows: 90% Caucasian, 5% Black and 5% Asian. The age range of participants was between 19 to 49 years of age with a mean of 28 years. See table below.

Table 6: Demographic Information

Trait		Female	Male	Overall
Gender	Female	.	.	12
	Male	.	.	9
Race	Asian	1	.	1
	Black	.	1	1
	Caucasian	11	8	19
Frame Size	Small	2	.	2
	Medium	7	9	16
	Large	3	.	3
Age	Mean	27	28	28
	S.D.	10	10	10
	Minimum	19	20	19
	Maximum	49	47	49
	N	12	9	21
Weight (lb)	Mean	144.8	177.8	159.0
	S.D.	21.0	16.1	25.0
	Minimum	107.0	156.0	107.0
	Maximum	178.0	206.0	206.0
	N	12.0	9.0	21.0
Height (in)	Mean	66.2	72.7	69.0
	S.D.	3.3	2.3	4.4
	Minimum	60.0	68.0	60.0
	Maximum	71.0	76.0	76.0
	N	12.0	9.0	21.0

Sponsor's Table

7.2.1.3 Extent of Exposure (dose/duration)

This study is a single-dose, 3-way crossover design with each treatment separated by a one week washout period. Twenty (20) subjects were exposed to two doses of Reglan [redacted] 10 mg; 21 subjects were exposed to one dose of Reglan 10 mg tablets.

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
The post-marketing safety experience of Reglan reported since December 2001 consists mainly of labeled adverse events, reflected in the prescribing information of Reglan.

7.2.3 Adequacy of Overall Clinical Experience

The metoclopramide tablet form has been previously approved for the short-term

(4-12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux disease (GERD) who fail to respond to conventional therapy and for the relief of symptoms associated with acute and recurrent diabetic gastroparesis. The regimen used in the indications proposed are already approved and currently being used. Overall, there is an adequate clinical experience with this drug that has been available in the market for 25 years now.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new animal data was submitted in this NDA.

7.2.5 Adequacy of Routine Clinical Testing

The sponsor performed the appropriate safety monitoring and clinical testing for patients in this study.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See Biopharmaceutics Review by Dr. Tien-Mien Chen.

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

The sponsor submitted a bioequivalence study in this NDA, the quality and completeness of the data are acceptable.

7.2.9 Additional Submissions, Including Safety Update

There were no additional submissions or safety update data submitted.

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

The only treatment-related adverse events reported in this trial for Reglan [redacted] is body ache in one patient (N=20), and for the reference listed drug, Reglan tablet, headache is reported in one patient (N=21). The number of patients in this trial is too small to draw conclusions regarding treatment related adverse events.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable.

7.4.2 Explorations for Predictive Factors

There is no new significant information regarding predictive factors that would affect the safety of the drug that is submitted in this NDA.

7.4.3 Causality Determination

Not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed indication and dosing regimen below for Reglan [redacted] 10mg is similar to the current dosing regimen of the reference listed drug (RLD), Reglan Tablet 10 mg. The safety and efficacy of these doses have been well-established.

For the Relief of Symptomatic Gastroesophageal Reflux

> Administer from 10 mg to 15 mg of REGLAN [redacted] ™ orally up to q.i.d. 30 minutes before each meal and at bedtime, depending upon symptoms being treated and clinical response. If symptoms occur only intermittently or at specific times of the day, use of metoclopramide in single doses up to 20 mg prior to the provoking situation may be preferred rather than continuous treatment. Occasionally, patients (such as elderly patients) who are more sensitive to the therapeutic or adverse effects of metoclopramide will require only 5 mg per dose.
>
> Experience with esophageal erosions and ulcerations is limited, but healing has thus far been documented in one controlled trial using q.i.d. therapy at 15 mg/dose, and this regimen should be used when lesions are present, so long as it is tolerated. Because of the poor correlation between symptoms and endoscopic appearance of the esophagus, therapy directed at esophageal lesions is best guided by endoscopic evaluation.
>
> Therapy longer than 12 weeks has not been evaluated and cannot be recommended.

For the Relief of Symptoms Associated with Diabetic Gastroparesis (Diabetic Gastric Stasis)

Administer 10 mg of REGLAN [redacted] ™ 30 minutes before each meal and at bedtime for two to eight weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation.

The sponsor also included in the label the instructions for use/handling of Reglan [redacted] It states "Just prior to administration, remove the REGLAN [redacted] ™ tablet from the bottle. Immediately place the tablet on top of the tongue where it will dissolve in seconds, then swallow with saliva. Administration with liquid is not necessary."

The dosing regimen proposed by the sponsor is acceptable as it is similar to the existing dosing regimen of the RLD. However, study SP759 have shown that Reglan 10 mg [redacted] disintegrates between 38 seconds and 233 seconds (3.8 minutes), with a median disintegration time of 63 seconds, and a mean of 81.43 seconds. See Table A1 in the Appendix section (10.1) for time to disintegration. Therefore, the claim that this drug "dissolves in seconds" maybe a misinformation to patients in whom Reglan [redacted] takes more than a minute to dissolve. Patients should be informed of the range of time it may take for this product to dissolve. This should be communicated in the package insert.

In addition, the orally disintegrating tablet proposed is scored, this will be a clinical concern in that patients might be encouraged to break or split the tablet in order to deliver a half dose. This will be a risk for inaccurate dosaging. Therefore, this Medical Officer highly recommends removing the scoring of this ODT formulation.

8.2 Drug-Drug Interactions

The label of metoclopramide states that 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.

The finding that metoclopramide releases catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

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

Gastroparesis (gastric stasis) may be responsible for poor diabetic control in some patients. Exogenously administered insulin may begin to act before food has left the stomach and lead to hypoglycemia. Because the action of metoclopramide will influence the delivery of

food to the intestines and thus the rate of absorption, insulin dosage or timing of dosage may require adjustment.

8.3 Special Populations

Metoclopramide is excreted in human milk; therefore, caution should be exercised when this drug is administered to a nursing mother.

In neonates, prolonged clearance may produce excessive serum concentrations. In addition, neonates have reduced levels of NADH-cytochrome b_5 reductase which, in combination with the aforementioned pharmacokinetic factors, make neonates more susceptible to methemoglobinemia.

Patients with NADH-cytochrome b_5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered.

The elderly may be at greater risk for tardive dyskinesia. Geriatric patients should receive the lowest dose of metoclopramide that is effective. Clinical studies of metoclopramide 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 increases with ascending dose. If parkinsonian-like symptoms develop in a geriatric patient receiving metoclopramide, metoclopramide should generally be discontinued before initiating any specific anti-parkinsonian agents. Sedation has been reported in metoclopramide users. Sedation may cause confusion and manifest as over-sedation in the elderly.

Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40 mL/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

8.4 Pediatrics

Safety and effectiveness in pediatric patients have not been established. The safety profile of metoclopramide 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.

Reglan is currently labeled for use in adults only and has no dosaging recommendations for the pediatric age group. This product, however, is being used substantially off-label by clinicians for the treatment of gastroesophageal reflux disease (GERD) in the pediatric population despite its lack of pediatric dosaging information in the label. This drug appears on the historical list of *Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population* for the indication of prevention of

chemotherapy-induced emesis, prevention of pos-operative nausea and vomiting, and treatment of symptomatic gastroesophageal reflux disease (GERD). Therefore, additional pediatric studies are necessary to provide additional dosing and safety information for this drug.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

The sponsor submitted a list of references/articles from peer reviewed journal and published articles. This reviewer has also searched the literature for information on metoclopramide and incorporated this information in the review.

8.7 Postmarketing Risk Management Plan

Not applicable.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

A comparison of the pharmacokinetics of metoclopramide orally disintegrating tablet, 10 mg (Reglan [redacted] ™) and metoclopramide tablets 10 (Reglan® tablets) in 21 healthy subjects (Study SP759) was conducted to support the following indications: short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy, and diabetic gastroparesis (diabetic gastric stasis).

The sponsor seeks approval of Reglan [redacted] ™ 5 and 10 mg under a 505(b)(1) application and relies on the Agency's finding of safety and efficacy for conventional Reglan® tablets. In this proposed new formulation, metoclopramide can be administered as orally disintegrating tablet formulation. The study conducted by showed that the Reglan [redacted] 10 mg formulation when given with or without water was bioequivalent to the reference Reglan® 10 mg tablet.

This study has also shown that Reglan [redacted] 10 mg has a similar safety profile when compared to the referenced listed drug, Reglan 10 mg tablet.

The combination of postmarketing data, previous clinical trials and adverse events analysis with study, SP759, establish the safety of Reglan [redacted] This metoclopramide orally disintegrating formulation will benefit patients who prefer not to take water after administering drugs or who have difficulty in swallowing tablets.

Reglan is currently labeled for use in adults only and has no dosaging recommendations for the pediatric age group. This product, however, is being used substantially off-label by clinicians for the treatment of gastroesophageal reflux disease (GERD) in the pediatric population despite its lack of pediatric dosaging information in the label. This drug appears on the historical list of *Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population* for the indication of prevention of chemotherapy-induced emesis, prevention of pos-operative nausea and vomiting, and treatment of symptomatic gastroesophageal reflux disease (GERD). Therefore, additional pediatric studies are necessary to provide additional dosing and safety information for this drug.

9.2 Recommendation on Regulatory Action

The approval of metoclopramide orally disintegrating tablet (Reglan [redacted] is recommended by this Medical Officer for the following indications:

- 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 gastric stasis.

For the indication of symptomatic gastroesophageal reflux failing to respond to conventional therapy, a dose of 10 mg to 15 mg of Reglan [redacted] orally up to q.i.d. 30 minutes before each meal and at bedtime is recommended.

For the indication of relief of symptoms associated with acute and recurrent diabetic gastric stasis, a dose 10 mg of Reglan [redacted] 30 minutes before each meal and at bedtime for two to eight weeks is recommended.

To get approval, the sponsor should incorporate the labeling recommendations listed in the Medical Officer's Labeling Review (see Appendix) and the NDA Team's labeling recommendations.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no risk management steps are recommended for this NDA.

9.3.2 Required Phase 4 Commitments

Metoclopramide has applicability to the pediatric population and it represents a meaningful therapeutic benefit especially in patients with gastroesophageal reflux disease (GERD) and diabetic gastroparesis. This Medical Officer recommends that the sponsor conduct efficacy and safety study that will supply information on the benefit of this drug in patients less than one year old and older than one year old. A PK/PD study to determine the appropriate dose in these populations is recommended prior to initiating the clinical outcome study.

9.3.3 Other Phase 4 Requests

No other Phase 4 requests are required.

9.4 Labeling Review

See line-by-line labeling review on section 10.2

9.5 Comments to Applicant

The sponsor should modify the label according to the NDA team's labeling recommendations.

The tablet scoring in this formulation should be removed so as not to encourage splitting or breaking the tablet.

10 APPENDICES

10.1 Tables

The times to disintegration for each subject for each of the two treatments are presented in the following table.

Table A1: Time to Disintegration (Seconds)

Subject	Treatment A	Treatment B
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
21		
Mean	80.70	82.15
SD	46.00	48.12
Minimum	[redacted]	
Median	61.00	64.50
Maximum	[redacted]	
N	20.00	20.00

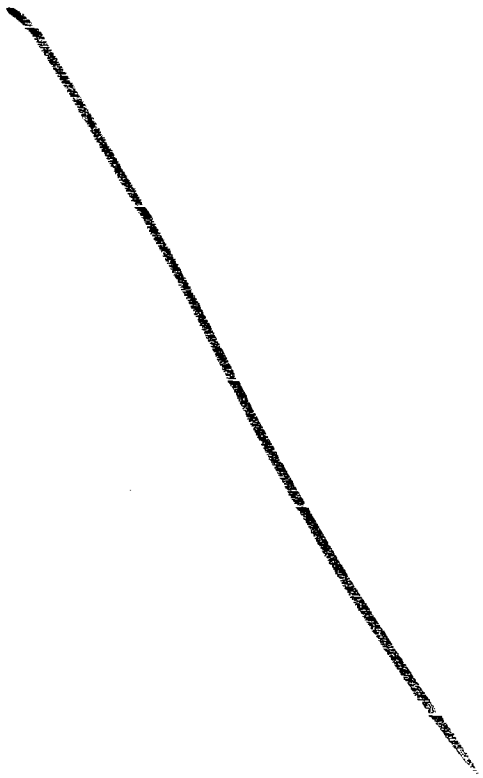
Sponsor's Table

Table A2: Overall Time to Disintegration (Seconds)

Mean	**81.43**
SD	**46.47**
Minimum	[redacted]
Median	**63.00**
Maximum	[redacted]
N	**40.00**

Sponsor's Table

10.2 Line-by-Line Labeling Review



Medical Officer Comments: No safety study was submitted with this NDA, the only trial conducted was a bioequivalence study in 21 healthy subjects. Therefore, due to the small number of patients who participated, it will be difficult to draw a general conclusion regarding safety; the statement above should be limited to the findings of the study.

[redacted]

In addition to the above line-by-line labeling comments, this Medical Officer concurs with the recommendations of the Division of Drug Marketing, Advertising, and Communications (DDMAC) and DMETS and should be communicated to the sponsor:

[redacted]