CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-793

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-793
Brand Name:	Reglan™
Generic Name:	Metoclopramide HCl
Dosage form and Strength:	Orally Disintegrating Tablets, 5 and 10 mg
Route of Administration:	Oral
Proposed Indications:	Symptomatic Gastroesophageal Reflux: 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 relief of symptoms associated with acute and recurrent diabetic gastric stasis (diabetic gastroparesis).
Proposed Dosage Regimen:	Symptomatic Gastroesophageal Reflux: 10 mg to 15 mg of REGLAN [redacted]™ orally up to q.i.d. 30 minutes before each meal and at bedtime Diabetic Gastroparesis (Diabetic Gastric Stasis): Administer 10 mg of REGLAN [redacted] ™ 30 minutes before each meal and at bedtime
Sponsor:	Schwarz Pharma
Type of Submission:	Original
Clinical Division:	Gastrointestinal and Coagulation Drug Products (HFD-180)
OCPB Division:	DPE II (HFD-870)
Priority:	Standard
Submission Date:	07/30/04
Reviewer:	Tien-Mien Chen, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.

I. Executive Summary

Currently, there is no orally disintegrating tablet (ODT) dosage form of metoclopramide on the market. On 07/30/04, Schwarz Pharma submitted original NDA 21-793 under 505(b)(1) seeking approval for Reglan™ (metoclopramide HCl) 5 and 10 mg ODT.

A bioequivalence (BE) study (SP759) conducted in 21 healthy male and female subjects comparing Reglan™ 10 mg ODT (placed on the tongue and swallowed without water after disintegration) with the currently marketed Schwarz Pharma's Reglan® (metoclopramide HCl) immediate release (IR) 10 mg oral tablet (swallowed with 240 mL water) under fasting conditions demonstrated BE of the two products. A biowaiver request for the lower strength, 5 mg ODT, can be granted since both 5 and 10 mg strengths of Reglan™ ODT are compositionally proportional and show similar dissolution characteristics.

The proposed dosing regimen for Reglan™ ODT is the same as Reglan® IR tablets and there is no new indication proposed for Reglan™ ODT. The biowaiver request for the food effect study can be granted. The waiver request for pediatric study was denied, instead, a deferral is granted.

A. Recommendations

NDA 21-793, Reglan™ (metoclopramide orally disintegrating tablets) 5 and 10 mg, submitted on 07/30/04 has been reviewed by Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II. It is acceptable from OCPB/DPE II perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the proposed package insert (p. 12, labeling comments) and dissolution specifications (below).

The proposed dissolution specifications for Reglan™ ODT need to be tightened as follows:

NLT [redacted] (Q) in 15 minutes

B. Phase IV Commitments: None

II. Table of Contents

III. Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

On 07/30/04, Schwarz Pharma submitted an original NDA 21-793 under 505(b)(1) regulations seeking approval for Reglan''' (metoclopramide) 5 and 10 mg ODT. One BE study was conducted comparing Reglan''' 10 mg ODT with Reglan® IR 10 mg tablet. To support a biowaiver for the lower strength, 5 mg Reglan™ ODT, *in vitro* dissolution data using three different dissolution media was also submitted. The proposed dosing regimen for Reglan''' ODT is the same as for Reglan® tablet and there is no new indication proposed.

The BE study SP759 was a randomized, single-dose, open-label, 3x3 crossover study comparing test product, Reglan™ 10 mg ODT administered with (Treatment A) and without 240 mL water (Treatment B) vs. the reference, Reglan® 10 mg IR tablet (Treatment C) with 240 mL water under fasting conditions with a washout period of one week in 21 healthy subjects (9 males and 12 females). Twenty subjects completed the study.

The results of the BE study demonstrated that Reglan™ 10 mg ODT is bioequivalent to the currently marketed Reglan® 10 mg IR tablet under fasting conditions based on the Agency's 2-1-sided BE acceptance criteria. The *in vitro* dissolution comparisons also showed comparable dissolution data and profiles **1)** between Reglan™ 10 mg ODT and Reglan® 10 mg IR and **2)** between Reglan™ 5 mg and 10 mg ODT. Biowaiver for the lower strength of Reglan™ 5 mg ODT can therefore be granted.

No food effect study is needed for Reglan''' ODT dosage form, therefore, the biowaiver request for the food effect study can be granted. The waiver request for pediatric study was denied, instead, a deferral was granted.

IV. Question Based Review

A. General Attributes

For prescription use, metoclopramide HCl is currently available as Reglan® injectable dosage form (5 mg/mL) owned by Baxter Healthcare Corp. and Reglan® oral IR tablet (5 and 10 mg) dosage forms on the market. Generic products of metoclopramide HCl are also available, i.e., injectable (5 mg/ml), oral solution (5 and 10 mg/ml), and oral IR tablet (5 and 10 mg) dosage forms. On 12/27/01, Schwarz Pharma acquired Reglan® 5 and 10 mg oral IR tablets (NDA 17-854), the reference listed drug. A pre-NDA meeting was held between Schwarz Pharma and Agency on 11/08/02 to discuss the proposed NDA for Reglan™ 5 and 10 mg ODT.

Schwarz Pharma is seeking approval for Reglan™ (metoclopramide HCl) 5 and 10 mg ODT, under 505(b)(1) provisions. This NDA relies on the Agency's finding of safety and efficacy of Reglan® 5 and 10 mg oral IR tablets. As such, there are no proposed changes to the indications and administration schedule. In support of the NDA, a single dose BE study (SP759) comparing the approved Reglan® IR Tablets 10 mg (reference) and Reglan™ 10 mg ODT (test) was conducted.

A biowaiver with supportive *in vitro* dissolution data is sought for Reglan™ 5 mg ODT as the 5 mg and 10 mg strengths are compositionally proportional. A biowaiver for food effect study and a waiver for pediatric study are also requested.

B. General Clinical Pharmacology

Metoclopramide 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. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs.

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.

For 1) the relief of symptomatic gastroesophageal reflux, 10 mg to 15 mg dose of Reglan™ ODT should be given up to q.i.d. 30 minutes before each meal and at bedtime and 2) the relief of symptoms associated with diabetic gastroparesis (diabetic gastric stasis), 10 mg of Reglan™ ODT should be given, 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.

C. Intrinsic Factors: Not Applicable

D. Extrinsic Factors: Not Applicable

E. General Biopharmaceutics:

Q: Is Reglan™ 10 mg ODT bioequivalent to Reglan® 10 mg tablet ?

Yes, Reglan™ 10 mg ODT swallowed after tablet disintegration on the tongue without water or with 240 mL of water is bioequivalent to Reglan® 10 mg tablet swallowed with 240 mL water.

Study SP759 was a randomized, single-dose, open-label, 3x3 crossover study with a washout period of one week in 21 healthy subjects (9 males and 12 females) under fasting conditions with the following treatments:

Treatment A: Reglan™ 1 x 10 mg ODT administered (placed on the tongue till disintegration and then swallowed with 240 mL water)

Treatment B: Reglan™ 1 x 10 mg ODT administered (placed on the tongue till disintegration and then swallowed without water)

Treatment C: Reglan® 1 x 10 mg tablet (swallowed with 240 mL water)

Twenty subjects completed the study. Reglan™ ODT 10 mg tablets placed on the tongue until disintegration and either swallowed without water (Test of interest- Treatment B) or swallowed with 240 mL water (Treatment A) is bioequivalent to the Reglan® 10 mg tablet (Reference-Treatment C) based on the Agency's recommended acceptance criteria, two one-sided tests procedure. Shown in Table 1 is the primary comparison of interest, Treatment B vs. C.

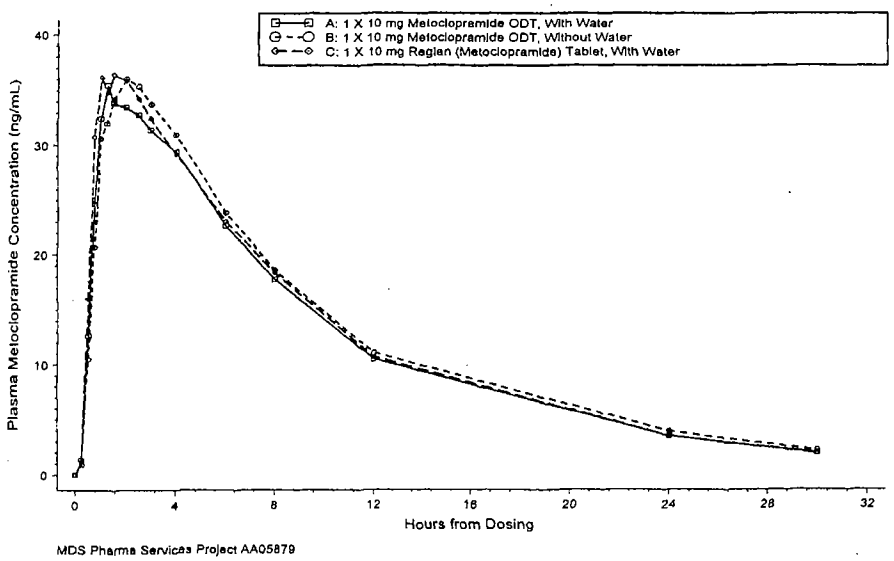
Table 1. Results of BE Assessment for Treatment B (Test of interest) vs. Treatment C (Reference)

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 (0.34)	3.61 (0.35)	3.67 (0.32)	94.9	88.7-101.6
Ln ($AUC_{0\text{-last}}$)[2]	5.81 (0.38)	5.85 (0.40)	5.84 (0.37)	100.5	96.2-104.9
Ln ($AUC_{0\text{-}\infty}$)[2]	5.87 (0.40)	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).

The mean plasma concentration time profiles of three treatments are shown in Figure 1.

Figure 1. Mean Plasma Profiles of Treatments, A, B and C.



Food effect:

For Reglan® oral tablets, food effect information is absent in the package insert. Food may affect the dissolution process of an oral dosage form. Since Reglan™ ODT is to be placed on the tongue till disintegration and then swallowed with saliva, additional dissolution process in the stomach may not be needed and therefore, sponsor's request for a biowaiver for the food effect study can be acceptable.

Time to disintegrate on the tongue:

For both Treatments A and B, the mean (± SD) times for Reglan™ ODT to disintegrate on the tongue were i.e., 80.7 ± 46.0 seconds and 82.2 ± 48.1 seconds, respectively. The above mean times for Reglan™ ODT are relatively long and should be described in the package insert. The individual data is shown below in Table 2:

Table 2. Individual Time of Disintegration (in second)

Treatment	A	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		
Median	61.00	64.50
Maximum		
N	20.00	20.00

Inspection:

The Division of Scientific Investigations (DSI) had conducted the audit on the BE study SP759 and the audit report has been submitted to GI Division on 03/18/05 (see DSI review dated 03/17/05 for details). DSI recommended reanalysis of some data points due to instability of analytical equipment. Reanalysis was performed by this reviewer and the reanalysis still met the Agency's BE acceptance criteria.

Formulation Composition:

The composition of the Reglan™ 5 and 10 mg ODT formulation are shown in Table 3. The two strengths are compositionally proportional.

Table 3. The Composition and Formulation of Reglan™ 5 and 10 mg ODT

REGLAN RPT, 5 mg

Ingredient Name	Role	% w/w per Tablet	Quantity (mg/tablet)
Coated Metoclopramide (15.6% active)[1]		17.32	32.04
Mannitol EZ, USP[2]			
Mannitol 60, USP/EP/JP			
Crospovidone,NF/EP/JP			
Microcrystalline Cellulose, NF/EP/JP			
Aspartame, NF/EP/JPE			
Magnesium Stearate, NF/EP/JP			
Natural & Artificial Orange Flavor, SN027512			
Colloidal Silicon Dioxide, NF/EP			
Total		**100.00**	

REGLAN [redacted] 10 mg

Ingredient Name	Role	% w/w per Tablet	Quantity (mg/tablet)
Coated Metoclopramide (15.6% active)[1]	Active	17.32	
Mannitol EZ, USP[2]			
Mannitol 60, USP/EP/JP			
Crospovidone,NF/EP/JP			
Microcrystalline Cellulose, NF/EP/JP			
Aspartame, NF/EP/JPE			
Magnesium Stearate, NF/EP/JP			
Natural & Artificial Orange Flavor SN027512			
Colloidal Silicon Dioxide, NF/EP			
Total		**100.00**	

[1] Quantity per batch is based on the coated metoclopramide theoretical potency of [redacted] active.
[2] The actual amount of mannitol EZ to be used in the batch will be based on the coated metoclopramide assay value.

Dissolution Data:

The proposed dissolution methodology and specification are as follows:

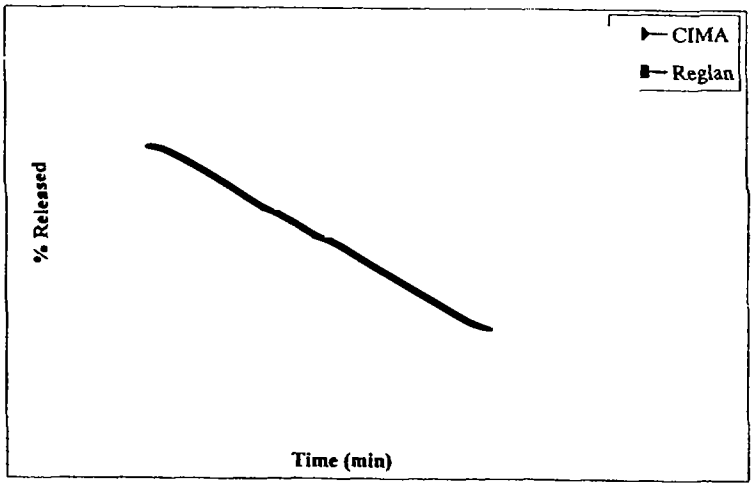
Medium: **pH 4.5, 0.1 M acetate buffer 900 mL at 37°C**
Apparatus: **USP Apparatus 2 (paddles)**
Paddle Speed: 25 rpm
Sample Size: n=12
Sampling at: 5, 10, 15, 30, and 45 min
Specifications: NLT [redacted] at 30 min

The dissolution data for the Test lot (730515) and Reference lot (3253902) used clinically in the BE study is shown in Table 4 and Figure 2 below:

Table 4. **Mean (± SD) Dissolution Data of The Test and Reference Lots (n=12/lot)**

Time (min)	% Released	
	10 mg IR Tablets	10 mg ODT
5		
10		
15		
30		
45		
f2		

Figure 2. **Mean Dissolution Profiles of The Test and Reference Lots**



The dissolution for both products is essentially complete in 30 minutes, indicating rapid dissolution for both products. The dissolution specifications for the Reglan''' ODT should therefore, be tightened as follows:

NLT ▬ (Q) in 15 minutes

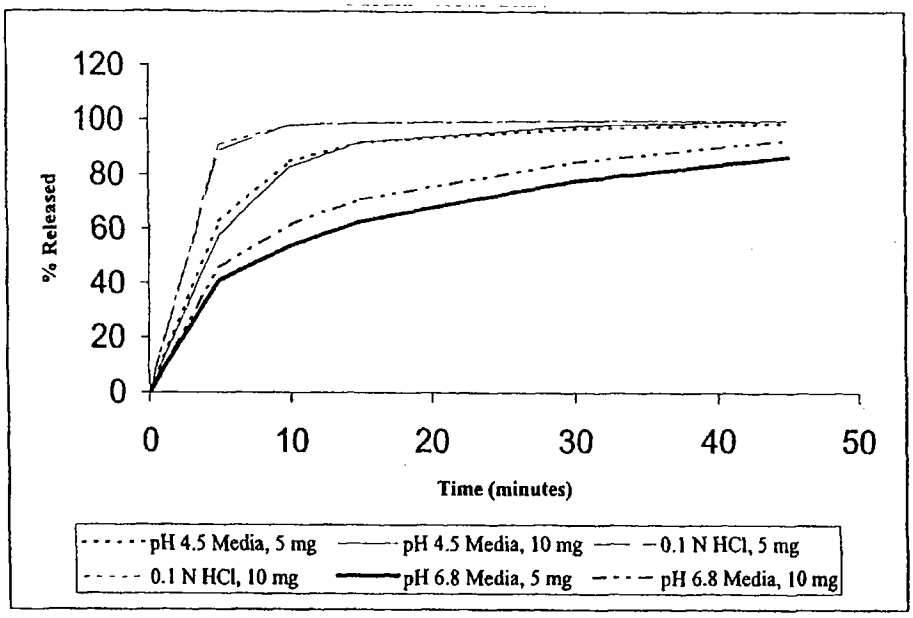
Comparative dissolution data (n=12/lot) for Reglan™ 5 mg (lot No. 730514) and 10 mg (lot No. 730515) ODT was also provided using three dissolution media (0.1N HCl, Acetate buffer pH 4.5, and Phosphate buffer pH 6.8) to support the biowaiver for the lower strength, 5 mg ODT.

Table 5. Comparative Mean Dissolution Data (12/lot) on Reglan''' **5 and 10 mg ODT in Different Dissolution Media**

Dissolution Mean (±SD)	0.1 N HCl		pH 4.5 Acetate Buffer		pH 6.8 Phosphate Buffer	
	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg
5 min	89 (4)	91 (4)	63 (7)	58 (4)	41 (4)	46 (6)
10 min	98 (4)	98 (2)	85 (4)	83 (3)	54 (5)	62 (3)
15 min	99 (3)	99 (2)	92 (4)	92 (3)	63 (4)	71 (3)
30 min	100 (3)	100 (2)	97 (4)	98 (3)	78 (4)	85 (3)
45 min	100 (3)	100 (2)	99 (5)	100 (3)	87 (4)	93 (4)
f2	94		79		58	

The above dissolution data showed that 5 and 10 mg ODT are similar in all thee media (similarity factor f2 values being 94, 79, and 58, respectively). The mean dissolution profiles are shown below:

Figure 3. Mean Dissolution profiles of Reglan''' 5 and 10 mg ODT



Since the 5 and 10 mg ODT are compositionally proportional and have demonstrated similar dissolution characteristics, the biowaiver for the lower strength of 5 mg Reglan" 'ODT can be granted.

F. Analytical Section: (The assay method was adequately validated.)

Blood samples (7 mL each) were [redacted]
20°C, transported to, and remained frozen until analyzed at bioanalytical site, [redacted]

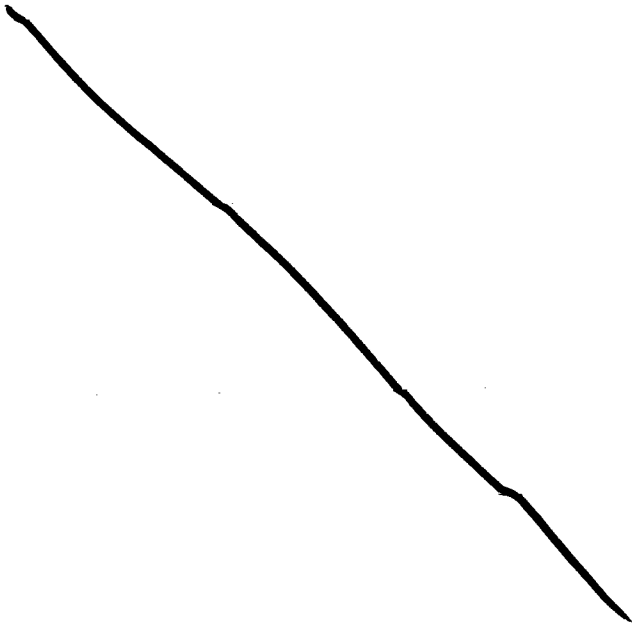
Method:	A validated LC/MS/MS method
Standard Curve:	1.0, 2.0, 5.0, 10.0, 20.0, 40.0, 75.0, 100.0, 125.0, 150.0 ng/mL
Precision:	2.9% to 8.6%
Accuracy:	-4.4% to 3.0%
LOQ:	1 ng/mL
QC Validation:	3, 60.0, 120.0 ng/mL
Precision:	7.0% to 16.6%
Accuracy:	0.8% to 7.7 %
QC Inter-batch Variation:	
Precision:	5.0% to 8.8%
Accuracy:	1.8% to 3.3%
QC Intra-batch Variation:	
Precision:	4.9% to 8.1%
Accuracy:	-3.3% to 1.8%

V. Labeling Recommendations

The following comments need to be conveyed to the sponsor. Please also see Appendix 1 for details, Agency's addition (being blue and underlined) and deletion (being red and double strikethrough).

1.

2.



3.

VI. Appendices

1. Proposed Package Insert (Original, 05/17/04 Version)

2. Study Synopsis (No. SP759)

3. Cover Sheet and OCPB Filing/Review Form

NDA 21-793 for Reglan™ (Metoclopramide) 5 and 10 mg Orally Disintegrating Tablets

Appendix 1

Sponsor's Proposed Labeling (05/17/04 Version)

13 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-*1

NDA 21-793 for Reglan• •(Metoclopramide) 5 and 10 mg Orally Disintegrating Tablets

Appendix 2

Synopsis of BE Study SP759

SYNOPSIS

TITLE:	A Pharmacokinetic Study to Determine the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT), of Metoclopramide HCl 10 mg Base and a Marketed Immediate Release Metoclopramide HCl Formulation (Reference), Reglan®, 10 mg Base, by Schwarz Pharma, Inc.
SPONSOR:	Schwarz Pharma, Inc. Mequon, WI 53092-4751
STUDY SITE:	[redacted]
INVESTIGATOR:	Alan S. Marion, MD, PhD
OBJECTIVES:	The objective of this study was to assess the single dose bioequivalence of the test product, 10 mg base metoclopramide HCl ODT formulation (manufactured by [redacted] for Schwarz Pharma, Inc.), and the reference product, Reglan® (10 mg base metoclopramide HCl, Schwarz Pharma, Inc.), when administered following a single 10 mg dose in the fasted state.
STUDY DESIGN:	This study had a randomized, single-center, single-dose, 3-way crossover, open-label design.
STUDY PHASE:	Phase I
NUMBER OF SUBJECTS:	A total of 21 subjects, 9 males and 12 females, were enrolled in the study, and 20 subjects, 9 males and 11 females, completed the study.

TREATMENTS:

A, B: Metoclopramide HCl ODT 10 mg base tablets
Manufactured by [redacted]
Lot No.: 730515
Manufacture date: Oct 2003

Subjects randomized to Treatment A received a single oral dose of one metoclopramide HCl ODT 10 mg base tablet taken with 240 mL of water after dissolution.

Subjects randomized to Treatment B received a single oral dose of one metoclopramide HCl ODT 10 mg base tablet with no water after dissolution.

C: Reglan® (metoclopramide HCl tablets, USP) 10 mg base tablets
Manufactured by Schwarz Pharma, Inc.
Lot No.: 3253902
Expiration date: May 2005

Subjects randomized to Treatment C received a single oral dose of one Reglan® tablet taken with 240 mL of water.

PK MEASURES AND METHODS:

The pharmacokinetics of metoclopramide were assessed by measuring serial plasma concentrations following administration of 10 mg base metoclopramide HCl as the test ODT formulation administered either with water (Treatment A) or without water (Treatment B), and as the reference product, Reglan® (Treatment C).

The pharmacokinetic parameters Cmax, Tmax, AUC(0-t), AUC(0-inf), AUCR [ratio of AUC(0-t) to AUC(0-inf)], Kel, and T1/2 were calculated using noncompartmental methods.
A parametric (normal-theory) general linear model was applied to the logarithmic transformations of the Cmax, AUC(0-t), and AUC(0-inf) values. The 90% confidence intervals (CI) of the ratios of the treatment geometric least-squares (LS) means (each

test/reference) were determined, and bioequivalence of each test treatment was assessed based on these 90% CI falling within the range of 80% to 125%.

RESULTS: The arithmetic means and standard deviations of plasma metoclopramide pharmacokinetic parameters and statistical comparisons of ln-transformed Cmax, AUC(0-t), and AUC(0-inf) following Treatments A and C are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Plasma Metoclopramide for Treatments A and C

	Plasma Metoclopramide					
	Treatment A		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax (ng/mL)	38.7	14.1	41.1	14.3		
Tmax (hr)	1.65	0.575	1.65	0.542		
AUC (0-t) (ng*hr/mL)	356.8	147.1	367.7	136.3		
AUC (0-inf) (ng*hr/mL)	383.9	179.4	391.7	154.4		
T1/2 (hr)	6.938	1.676	7.053	1.261		
Kel (1/hr)	0.1046	0.02160	0.1009	0.01600		
AUCR	0.9419	0.03932	0.9442	0.02371		
ln(Cmax)	3.597	0.3441	3.665	0.3169	87.28- 99.91	93.4
ln[AUC(0-t)]	5.807	0.3748	5.843	0.3689	92.28-100.62	96.4
ln[AUC(0-inf)]	5.867	0.3991	5.901	0.3805	92.44-101.18	96.7

Treatment A = 1 X 10 mg Metoclopramide ODT, With Water: test
Treatment C = 1 X 10 mg Reglan (Metoclopramide) Tablet, With Water: reference

Appears This Way On Original

The arithmetic means and standard deviations of plasma metoclopramide pharmacokinetic parameters and statistical comparisons of ln-transformed Cmax, AUC(0-t), and AUC(0-inf) following Treatments B and C are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Plasma Metoclopramide for Treatments B and C

	Plasma Metoclopramide					
	Treatment B		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax (ng/mL)	39.2	13.9	41.1	14.3		
Tmax (hr)	1.88	0.713	1.65	0.542		
AUC(0-t) (ng*hr/mL)	374.3	167.2	367.7	136.3		
AUC(0-inf) (ng*hr/mL)	406.9	208.1	391.7	154.4		
T1/2 (hr)	7.386	1.907	7.053	1.261		
Kel (1/hr)	0.09870	0.02067	0.1009	0.01600		
AUCR	0.9346	0.04094	0.9442	0.02371		
ln(Cmax)	3.610	0.3533	3.665	0.3169	88.72-101.56	94.9
ln[AUC(0-t)]	5.845	0.3997	5.843	0.3689	96.21-104.91	100.5
ln[AUC(0-inf)]	5.913	0.4267	5.901	0.3805	97.11-106.29	101.6

Treatment B = 1 X 10 mg Metoclopramide ODT, Without Water: test
Treatment C = 1 X 10 mg Reglan (Metoclopramide) Tablet, With Water: reference

CONCLUSION: Pharmacokinetic and statistical analyses of the data resulting from the administration of a single 10 mg base metoclopramide HCl dose administered as the test ODT tablet, either with or without water, and as the reference tablet (Reglan®), have shown that under both administration conditions (with and without water) the test formulation has met the requirements for bioequivalence with the reference treatment. The 90% CI for the comparison of metoclopramide ln-transformed Cmax, AUC(0-t), and AUC(0-inf) were all within the acceptable range of 80% to 125% required for the conclusion of bioequivalence.

NDA 21-793 for Reglan• •(Metoclopramide) 5 and 10 mg Orally Disintegrating Tablets

Appendix 3

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-793	Brand Name	Reglan
OCPB Division (I, II, III)	DPE II	Generic Name	Metoclopramide
Medical Division	GI and Coagulation	Drug Class	To sensitize tissues to the action of acetylcholine
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	GI disorders
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Orally disintegrating tablet
		Dosing Regimen	10-15 mg up to QID 30 min before each meal and at bedtime
Date of Submission	07/30/04	Route of Administration	Oral
Estimated Due Date of OCPB Review	04/25/05	Sponsor	Schwarz Pharma
Medical Division Due Date	04/26/05	Priority Classification	3 S
PDUFA Due Date	06/10/05		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1	1	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Is Reglan® orally disintegrating tablet bioequivalent to Reglan® immediately release oral tablet?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**09/16/04**	
Secondary reviewer Signature and Date	**09/16/04**	

CC: NDA 21-793, HFD-850 (Electronic Entry or Lee), HFD-180 (S. Daugherty), HFD-870 (S. Doddapaneni, H. Malinowski, J. Hunt)

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/s/

Tien-Mien Chen
4/26/05 12:45:52 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
4/26/05 12:54:46 PM
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