CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-246

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

PRODUCT (Generic Name):	Metoclopramide
PRODUCT (Proposed Brand Name):	**METZOLV® ODT**
DOSAGE FORM:	Orally Disintegrating Tablet (ODT)
DOSAGE STRENGTH:	5 mg, 10 mg
NDA:	22-246
PROPOSED INDICATIONS:	Gastroesophageal Reflux Disease (GERD) and Diabetic Gastroparesis
NDA TYPE:	505(b) (2)
SUBMISSION DATE:	January 29, 2008
SPONSOR:	Wilmington Pharmaceuticals
REVIEWER:	Tapash K. Ghosh, Ph.D.
TEAM LEADER:	Sue-Chih Lee, Ph.D.
OCPB DIVISION:	DCP III, HFD 880
OND DIVISION:	HFD180

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   - **1.2 Phase 4 Commitments**
   - **1.3 Summary of Important Clinical Pharmacology Findings**

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1. Executive Summary

The sponsor, Wilmington Pharmaceuticals, has developed a novel formulation of metoclopramide (METZOLV®) claiming as orally disintegrating tablet (METZOLV® ODT) using Catalent Pharma Solutions, Inc.'s Zydis® fast dissolve technology. The proposed drug product represents the same strength (5 mg and 10 mg), route of administration (oral) and indications (GERD and diabetic gastroparesis) as the reference drug, Reglan® Tablets, 5 mg and 10 mg, but is a new formulation.

Previously another ODT formulation of metoclopramide, Reglan® ODT (5 and 10 mg) was approved (NDA21-793); however, no studies could be performed against the Reglan® ODT product since it is not commercially available.

One pilot (Study NA464) and two pivotal (Study 10643701 and N 10743701) clinical pharmacology studies were submitted in this application as described below. The pivotal studies only have been reviewed.

Pilot Study: An open label, 2-way crossover, randomized, single-center pharmacokinetic study in 12 healthy volunteers to compare the rate and profile of absorption of metoclopramide following 10 mg Zydis metoclopramide and 1 X 10 mg Reglan tablet (NA464)

Pivotal Study # 1: The Relative Bioavailability of Metoclopramide 10 mg Orally Disintegrating Tablets (Wilmington Pharmaceuticals) Compared to REGLAN® (metoclopramide) 10 mg Tablets (Schwarz Pharma) Under Fasting Conditions (Study 10643701)

Pivotal Study # 2: The Effect of Food on the Bioavailability of Metoclopramide 10 mg Orally Disintegrating Tablets (Wilmington Pharmaceuticals) and on its Relative Bioavailability with REGLAN® (metoclopramide) 10 mg Tablets (Schwarz Pharma) (Study 10743701)

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

The sponsor requested a waiver of the in vivo BA study for the 5 mg strength of METZOLV® ODT based on the demonstrated bioequivalence of the 10 mg METZOLV® ODT to the RD together with the formulation proportionality between the 5 mg and 10 mg strengths. Chemistry review will address this issue.

The sponsor evaluated *in-vivo* disintegration time of the proposed formulation in the pivotal clinical studies (Study 10643701 and Study 10743701) mentioned above. However they described the study results as *in-vivo* dissolution time. For study like that, *in-vivo* disintegration time is commonly used as opposed to *in-vivo* dissolution time. Therefore, now onwards the sponsor's results reported as "*in-vivo* dissolution" will be described as "*in-vivo* disintegration" time. , The *in-vivo* disintegration data in these studies are alarming as 10% (10/96) had disintegration time above 2 minutes and especially as high as 13.75 minutes. In this reviewer's opinion, METZOLV® ODT defeats the purpose of an ODT. It should rather be taken by mouth with liquid like a conventional tablet if it does not disintegrate in the mouth in about a minute.

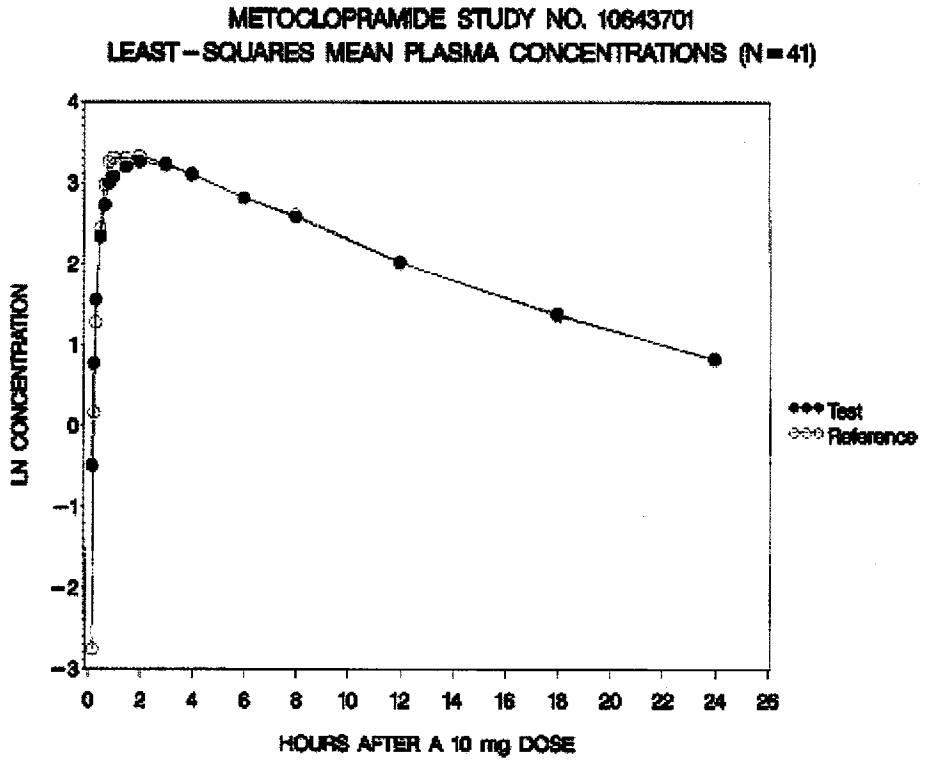
1.1 RECOMMENDATIONS

NDA 22-246, METZOLV® ODT (metoclopramide orally disintegrating tablets) 5 and 10 mg, submitted on January 27, 2007 has been reviewed by Office of Clinical Pharmacology /Division of Pharmaceutical Evaluation III (OCP/DCP III). The information for the 10 mg strength is acceptable from OCP/DPE III perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the proposed package insert. The biowaiver for the 5 mg strength is being reviewed by ONDQA.

1.2 Phase IV commitments: None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Bioequivalency: Based on the statistical analysis of metoclopramide, Wilmington Pharmaceuticals, LLC's METZOLV® ODT 10 mg tablets (Test) are bioequivalent to REGLAN® (metoclopramide) Tablets 10 mg (Reference by Schwarz Pharma, Inc.) under fasted conditions (Study 10643701).



Parameter	Least Squares Means [1]		Test/Ref. Ratio [2]	90% Confidence Interval [3]	
	Test A	Reference B		Lower	Upper
AUC 0-t (ng-hr/ml)	245.69	253.58	0.9689	0.9392	0.9987
AUC 0-inf (ng-hr/ml)	267.55	276.11	0.9690	0.9345	1.0035
Cmax (ng/ml)	27.90	30.33	0.9199	0.8765	0.9633
Kel (1/hour)	0.112	0.114	0.9809		
Elimhalf (hour)	6.38	6.30	1.0129		
Ln-Transformed Data					
AUC 0-t (ng-hr/ml)	238.04	244.60	0.9732	0.9456	1.0016
AUC 0-inf (ng-hr/ml)	258.30	264.71	0.9758	0.9447	1.0079
Cmax (ng/ml)	27.02	29.48	0.9165	0.8769	0.9579

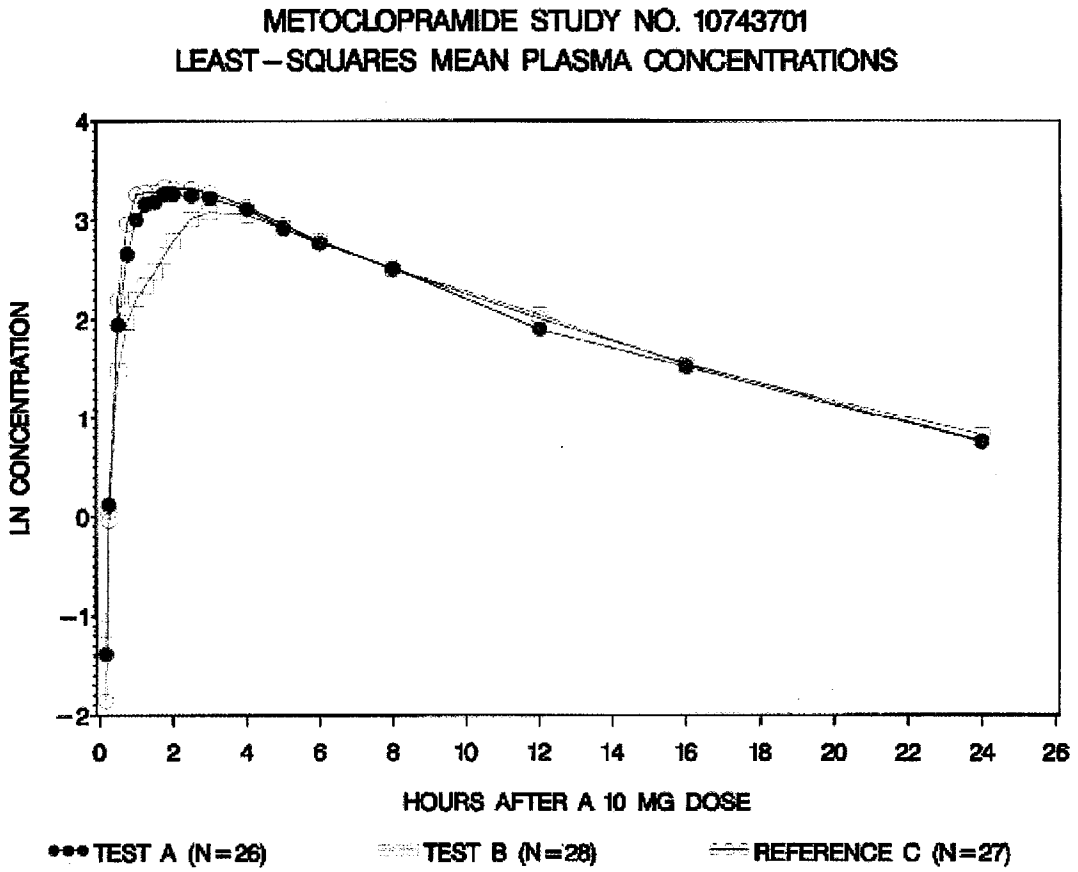
Tmax (hour)	**Median**
Test A	2.00
Reference B	1.50

AUC 0-t / AUC 0-inf ratio [4]	
Test A	0.9183
Reference B	0.9184

1 Least squares geometric means for ln-transformed data.
2 Test/Ref. Ratio calculated as Test mean divided by Reference mean.
3 Confidence interval on the ratio.
4 AUC 0-t / AUC 0-inf ratio calculated as AUC 0-t mean divided by AUC 0-inf mean.

Food Effect: Comparison between METZOLV ODT (Test) and the reference Reglan tablet (Reference) demonstrated that the overall bioavailability (LnAUC0-t and LnAUC0-inf) of METZOLV ODT 10 mg tablet compared to REGLAN® (metoclopramide) USP 10 mg Tablets (Schwarz Pharma, Inc.), was equivalent when both were taken in the fed state in terms of AUC. However, Cmax was approximately 24%

lower for the test product compared to the reference product when both were taken following a high fat meal. It should be noted that the labeling for REGLAN® (metoclopramide) USP 10 mg Tablets (Schwarz Pharma, Inc.) recommends that these tablets be taken approximately 30 minutes prior to eating (Study 10743701).



Study 107 Test B (Fed)/Test A (Fast) N=28					
Parameter	Test B (Fed)	Test A (Fast)	Ratio	90% CI Lower	90% CI Upper
AUC0-t	203.7954	223.0159	91.38	86.97	96.01
AUCinf	225.8384	240.4259	93.93	89.35	98.76
Cmax	22.8269	27.1247	84.16	78.31	90.44

Study 107 Test B (Fed)/Ref C (Fed) N=28					
Parameter	Test B (Fed)	Ref C (Fed/Reglan)	Ratio	90% CI Lower	90% CI Upper
AUC0-t	203.7954	234.3612	86.96	82.83	91.29
AUCinf	225.8384	253.1587	89.21	84.93	93.71
Cmax	22.8269	30.2197	75.54	70.37	81.08

***Test A** = METZOLV® ODT in fasting condition; **Test B** = METZOLV® ODT in fed condition; **Test C** = REGLAN® Tablet in fed condition.*

The *in-vivo* disintegration data in these studies are alarming as 10% (10/96) had disintegration time above 2 minutes and especially as high as 13.75 minutes. In this

reviewer's opinion, METZOLV® ODT defeats the purpose of an ODT. It should rather be taken by mouth with liquid like a conventional tablet.

Primary Reviewer: Tapash K. Ghosh, Ph.D.
Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation III

Team Leader: Sue-Chih Lee, Ph. D._____

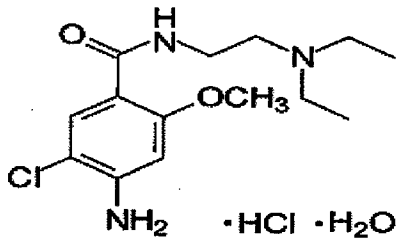
2. Question Based Review

2.1. General Attributes

2.1.1. What are the chemical and physical-chemical properties of the drug substance?

Trade name: Metozolv ODT
Generic name: Metoclopramide Orally Disintegrating Tablet
Chemical name: 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate
Molecular formula: $C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$
Molecular weight: 354.3

Chemical Structure:



Dosage Form Description: The drug product is a white to off-white round freeze-dried tablet with a "5" or a "10" debossed on the tablet to include the tablet strength with the following composition:

Composition of the Drug Product				
Component	**Function**	**Amount (5 mg tablet)**	**Amount (10 mg tablet)**	**Amount (%w/w) per dried tablet**
Metoclopramide HCl (as the free base)	Active	5.000 mg[1]	10.00 mg[1]	(b) (4)
Gelatin NF				(b) (4)
Mannitol USP				
Mint Flavor (b) (4)				
Acesulfame Potassium NF				
(b) (4)				
Sodium Hydroxide USP				
Total				(b) (4)

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

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.

The proposed product, METZOLV® ODT, is indicated for Gastroesophageal Reflux Disease (GERD) and Diabetic Gastroparesis.

2.1.3. What is the proposed route of administration?

METOZOLV ODT is designed to be taken without liquid with dry hands and place on the tongue.

2.2. Clinical Pharmacology

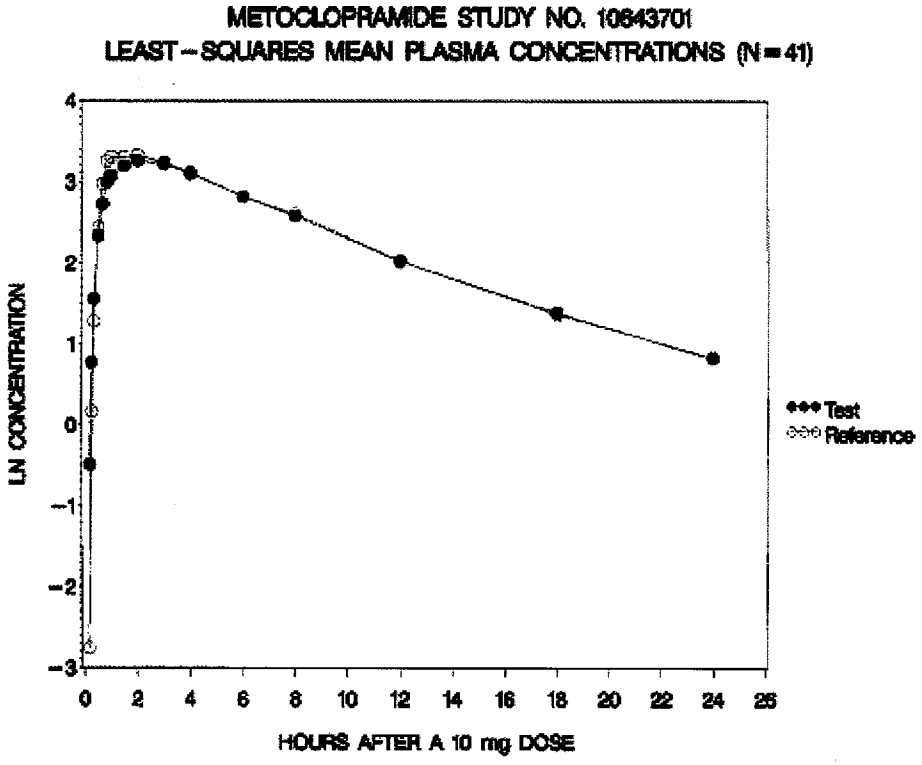
2.2.1: Is METZOLV® ODT 10 mg bioequivalent to Reglan® 10 mg tablet ?

Yes. In Study 10643701 entitled "The Relative Bioavailability of Metoclopramide 10 mg Orally Disintegrating Tablets (Wilmington Pharmaceuticals) Compared to REGLAN® (metoclopramide) 10 mg Tablets (Schwarz Pharma) Under Fasting Conditions."

This was a randomized, single-dose, two-way, cross-over study under fasting conditions comparing equal doses of the test and reference products administered to 44 normal, healthy adults with 41completing the study [M 32; F 9. Age: 30 ± 10.3 (range 19 – 54)]. Following an overnight fast of at least 10 hours, ODT (Test A: 1 x 10 mg tablet) was administered (at 0 hour) by placing the tablet directly on the subjects tongue under direct observation. Time taken from dosing until the tablet has completely disintegrated into fine partcicles were recorded on the source document and CRFs. No water was provided with the tablet or allowed for one hour prior or post dose. There was a 7-day interval between treatments.

The reference Reglan® Tablet (Reference B: 1 x 10 mg tablet) was administered (at 0 hour) with 240 ml of room temperature tap water after an overnight fast of at least 10 hours. Subjects were instructed to swallow the tablet whole without chewing or biting.

The time-concentration profile of test and reference in log scale is presented below:



The test to reference ratios and corresponding 90% confidence intervals for metoclopramide are given in the following table:

Parameter	Least Squares Means [1]		Test/Ref. Ratio [2]	90% Confidence Interval [3]	
	Test A	Reference B		Lower	Upper
AUC 0-t (ng-hr/ml)	245.69	253.58	0.9689	0.9392	0.9987
AUC 0-inf (ng-hr/ml)	267.55	276.11	0.9690	0.9345	1.0035
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Tmax (hour)	**Median**
Test A	2.00
Reference B	1.50

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1 Least squares geometric means for ln-transformed data.
2 Test/Ref. Ratio calculated as Test mean divided by Reference mean.
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4 AUC 0-t / AUC 0-inf ratio calculated as AUC 0-t mean divided by AUC 0-inf mean.

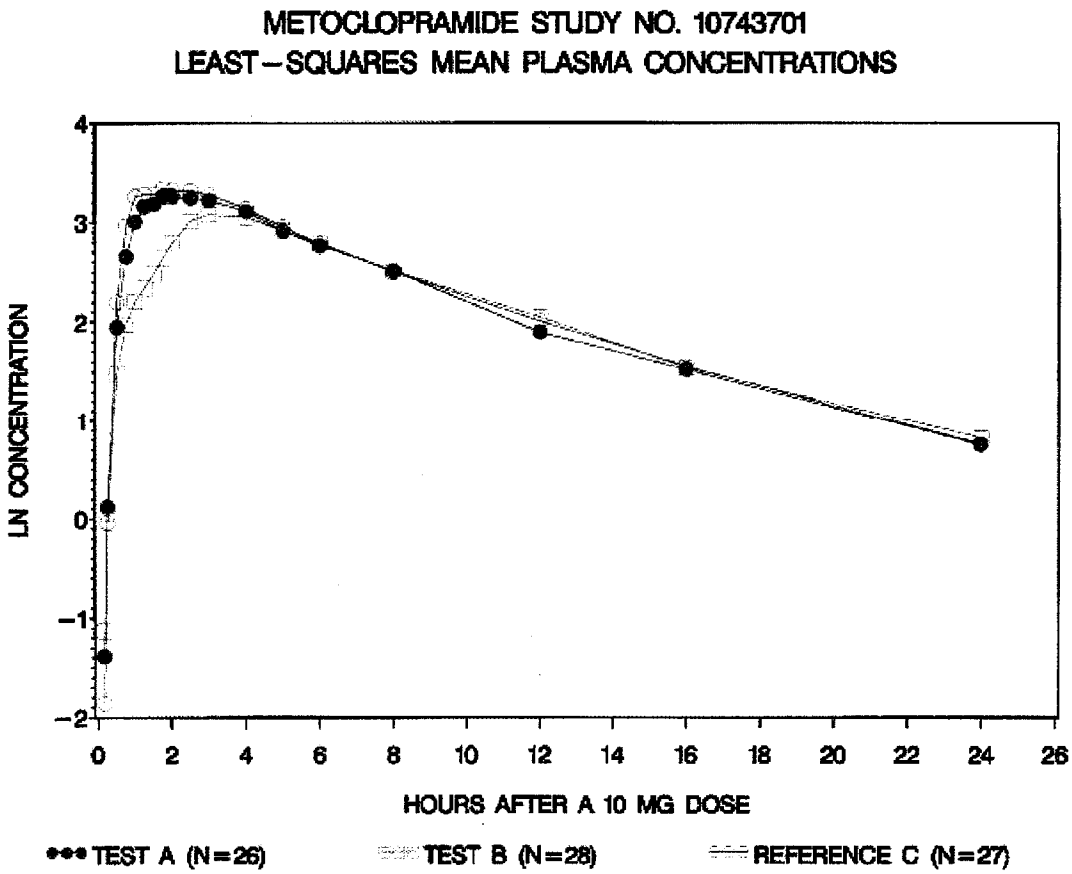
Based on the statistical analysis of metoclopramide, Wilmington Pharmaceuticals, LLC's METZOLV® ODT 10 mg tablets are bioequivalent to REGLAN® (metoclopramide) Tablets 10 mg (Schwarz Pharma, Inc.) under fasted conditions.

2.2.2: What is the Effect of Food on METZOLV® ODT 10 mg?

In Study 10743701, the sponsor investigated the Effect of Food on the Bioavailability of Metoclopramide 10 mg Orally Disintegrating Tablets (Wilmington Pharmaceuticals) and on its Relative Bioavailability with REGLAN® (metoclopramide) 10 mg Tablets (Schwarz Pharma). This randomized, single-dose, three-treatment, three-period, crossover study with 30 (28 subjects completing at least two periods of the study) healthy adults was conducted to compare two formulations of 10 mg metoclopramide tablets, under fasting and fed conditions. Subjects received the test product METZOLV® ODT in one study period following an overnight fast of at least 10.5 hours (Test A) and in a second period following the FDA standardized breakfast preceded by an overnight fast of at least 10 hours (Test B). In a third period, subjects received the reference product REGLAN® (metoclopramide) USP 10 mg Tablets (Schwarz Pharma, Inc.) following the FDA standardized breakfast preceded by an overnight fast of at least 10 hours (Reference C). There was a 7-day interval between treatments.

Test A:	Metoclopramide Orally Disintegrating 10 mg tablets (Wilmington Pharmaceuticals, LLC) administered after an overnight fast
Test B:	Metoclopramide Orally Disintegrating 10 mg tablets (Wilmington Pharmaceuticals, LLC) administered after a standardized high fat breakfast
Reference C:	REGLAN® (metoclopramide) tablets 10 mg (Schwarz Pharma) administered after a standardized high fat breakfast

The time-concentration profile of test and reference in log scale is presented below:



Test A = METZOLV® ODT in fasting condition; Test B = METZOLV® ODT in fed condition; Test C = REGLAN® Tablet in fed condition.

The test to reference ratios and corresponding 90% confidence intervals for metoclopramide are given in the following tables:

Study 107 Test B (Fed)/Test A (Fast) N=28					
Parameter	Test B (Fed)	Test A (Fast)	Ratio	90% CI Lower	90% CI Upper
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AUCinf	225.8384	253.1587	89.21	84.93	93.71
Cmax	22.8269	30.2197	75.54	70.37	81.08

The overall oral bioavailability of METZOLV® ODT as evaluated using $LnAUC_{0\text{-}t}$, $LnAUC_{0\text{-}inf}$ demonstrated that total exposure (as measured by AUC) are within the BE

criteria with or without food. However, peak plasma concentrations (Cmax) were reduced by about 17% when METZOLV® ODT was taken following high fat breakfast. Comparison between METZOLV ODT and the reference Reglan tablet demonstrated that the overall bioavailability (LnAUC0-t and LnAUC0-inf) of METZOLV ODT 10 mg tablet compared to REGLAN® (metoclopramide) USP 10 mg Tablets (Schwarz Pharma, Inc.), was equivalent when both were taken in the fed state in terms of AUC. However, Cmax was approximately 24% lower for the test product compared to the reference product when both were taken following a high fat meal. It should be noted that the labeling for REGLAN® (metoclopramide) USP 10 mg Tablets (Schwarz Pharma, Inc.) recommends that these tablets be taken approximately 30 minutes prior to eating.

2.2.3: What is the in-vivo disintegration time on the tongue?

In study 10643701, (N = 41), mean in-vivo disintegration time was 91 (± 164.83) seconds with median value of 45 seconds and range between 10 - 825 seconds. 90% (N=37) of the subjects had a disintegration time of 120 seconds or less and 73% (N = 30) of the subjects had a disintegration time of 60 seconds or less.

In study 10743701, (N = 55), mean in-vivo disintegration time was 66 (± 33.43) seconds with median value of 59 seconds and range between 19 - 157 seconds. 91% (N=50) of the subjects had a disintegration time of 120 seconds or less and 53% (N = 29) of the subjects had a disintegration time of 60 seconds or less.

Overall the *in-vivo* disintegration parameters are as follows:

Parameters	**Value (secs)**
N	96
Mean	76.77
Median	53.50
SD	110.62
%CV	144.09
Max	825.00
Min	10.00

Overall, the *in-vivo* disintegration data in these studies are alarming as 10% (10/96) had disintegration time above 2 minutes and especially as high as 13.75 minutes. In this reviewer's opinion, METZOLV® ODT defeats the purpose of an ODT. It should rather be taken by mouth with liquid like a conventional tablet.

2.2.4: Inspection:

DSI inspection Report on Pivotal BE Study 10643701 pending.

2.2.5. What are the pharmacokinetics of metoclopramide?

This is a 505 (b)(2) application which relies, in part, on FDA's findings of safety and efficacy of the reference product, Reglan® (metoclopramide tablets USP) 5 mg and 10 mg, approved NDA 17, 854 held by the Schwarz Pharma as well as the safety and efficacy information contained in the published scientific literature. They did not conduct any basic pharmacokinetic (PK) study in this NDA other than the two studies, BE and food-effect studies.

The following information is taken from the Regaln label. The absolute oral bioavailability of metoclopramide relative to an intravenous dose of 20 mg, is 80% ± 15.5% as demonstrated in a crossover study of 18 subjects. Peak plasma concentrations occur at about 1 to 2 hr after a single oral dose. Similar time to peak is observed after individual doses at steady state. A single dose study of 12 subjects showed that the area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination rate remains the same. The average elimination half-life in individuals with normal renal function is 5 to 6 hr. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

2.2.6. What are the pharmacokinetics of METOZOLV ODT ?

In a randomized, two-arm, two-way crossover study in 44 healthy adult (male and female) fasted subjects. METOZOLV ODT was bioequivalent to Reglan Tablets.

In a food-effect study with 28 subjects, METOZOLV ODT taken immediately after a high-fat meal had a 17% lower peak blood level than when taken after an overnight fast. The time to peak blood levels increased from about 1.75 hours under fasted conditions to 3 hours when taken immediately after a high fat meal. The extent of metoclopramide absorbed (area under the curve) was comparable whether METOZOLV ODT was administered with or without food. Food diminishes the peak metoclopramide blood levels attained with METOZOLV ODT and prolongs the time it takes to achieve a peak blood level. The clinical effect of the decrease in peak plasma level if Metozolv ODT is inadvertently taken with food is unknown.

2.2.7. What are the dose and dosing regimen?

Dosage forms & Strengths: **Orally Disintegrating Tablet: 5 and 10 mg**

- **Gastroesophageal Reflux Disease (GERD):** 10 mg to 15 mg dose up to four times daily at least 30 minutes before eating (2.1) and at bedtime. Therapy should not exceed 12 weeks in duration.

- **Diabetic Gastroparesis (Diabetic Gastric Stasis):** Take a 10 mg dose four times daily at least 30 minutes before eating (2.2) and at bedtime for two to eight weeks. Therapy longer than 12 weeks has not been evaluated and cannot be recommended.

2.3. Intrinsic Factors

METZOLV ODT 10 mg tablet is designed to be bioequivalent to reference product REGLAN® (metoclopramide) USP 10 mg Tablets and therefore, the influence of any intrinsic factors would be expected to be the same as indicated for REGLAN® (metoclopramide) USP 10 mg Tablets and are reflected in the label.

2.4. Extrinsic factors

Drug drug interactions with METZOLV ODT are expected to be the same as mentioned in the REGLAN® (metoclopramide) USP Tablets . However, food effect is formulation dependent and effect of food on METZOLV ODT has been studied and appropriate language has been suggested in the label.

2.5. Analytical

Were the correct moieties identified and properly measured?

Yes,

3. Detailed Labeling Recommendations:

The following text should be inserted into the labeling, as appropriate. Section in Red indicates suggested inclusion and ~~strike thorough~~ indicates suggested deletion.

DOSAGE & ADMINISTRATION

(b) (4)

(b) (4) 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. (b) (4) Metozolv ODT disintegrates on the tongue in approximately one minute with a range of 10 seconds to 14 minutes. (b) (4) 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.

CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics (PK)

Adult PK of METOZOLV ODT:

In a randomized, two-arm, two-way crossover study in 44 healthy adult (male and female) fasted subjects. METOZOLV ODT was bioequivalent to Reglan Tablets.

In a food-effect study with 28 subjects, METOZOLV ODT taken immediately after a high-fat meal had a 17% lower peak blood level than when taken after an overnight fast. The time to peak blood levels increased from about 1.75 hours under fasted conditions to 3 hours when taken immediately after a high fat meal. The extent of metoclopramide absorbed (area under the curve) was comparable whether METOZOLV ODT was administered with or without food. The clinical effect of the decrease in peak plasma level if Metozolv ODT is inadvertently taken with food is unknown.

Adult PK of Metoclopramide:

(b) (4)

TABLE 2: ADULT PHARMACOKINETIC DATA

PARAMETER	VALUE
VD (L/KG)	~ 3.5
PLASMA PROTEIN BINDING	~ 30%
T ½	5 TO 6 HOURS
ORAL BIOAVAILABILITY	80% ± 15.5%

Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 hr. Of the 85% eliminated in the urine, about half is present as free or conjugated metoclopramide.

The drug is not extensively bound to plasma proteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg) which suggests extensive distribution of drug to the tissues.

(b) (4)

Renal impairment affects the clearance of metoclopramide. In a study with patients with varying degrees of renal impairment, a reduction in creatinine clearance was correlated with a reduction in plasma clearance, renal clearance, non-renal clearance, and increase in elimination half-life. The kinetics of metoclopramide in the presence of renal impairment remained linear. The reduction in clearance as a result of renal impairment suggests that reduction of maintenance dosage should be done to avoid drug accumulation.

(b) (4)

(b) (4)

Pediatric PK

The pharmacodynamics of metoclopramide following oral and intravenous administration in pediatric populations are highly variable and a concentration-effect relationship has not been established. Thus, there are insufficient data to conclude whether the pharmacokinetics of METOZOLV ODT in adults and the pediatric population are similar. Although there are insufficient data to support the efficacy of METOZOLV ODT in pediatric patients with symptomatic gastroesophageal reflux disease (GERD) or cancer chemotherapy-related nausea and vomiting, the pharmacokinetics of Reglan have been studied in these patient populations and are summarized as follows.

In an open-label study, six pediatric patients (ranging in age from 3.5 weeks to 5.4 months) with GERD received metoclopramide 0.15 mg/kg oral solution every 6 hours for 10 doses. The mean peak plasma concentration of metoclopramide after the tenth dose was twice the level (56.8 μg/L) compared to after the first dose (29 μg/L) indicating drug accumulation with repeated dosing. However, the PK parameters after the tenth dose were comparable to those observed after the first dose for the mean time to reach peak concentrations (2.2 hr); half-life (4.1 hr); clearance (0.67 L/h/kg); and volume of distribution (4.4 L/kg). The youngest patient (3.5 weeks) showed a significantly longer half-life after the first dose (23.1 hr) compared to after the tenth dose (10.3 hr), suggesting the reduced clearance observed at birth may be a reflection of the immature hepatic and renal systems.

(b) (4)

(b) (4)

14 Pages Withheld as b(4) Draft Labeling

4.2 Individual Study Reviews

NDA: 22-246/Study 10643701 **Study Dates: Mar '06 – Apr '06**

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

Objectives: The purpose of this study was to evaluate the relative bioavailability of the test formulation of METZOLV® ODT 10 mg tablets (Lot No. 413808), with an already marketed reference formulation REGLAN® (metoclopramide) Tablets 10 mg (Schwarz Pharma, Inc.) under fasted conditions in healthy, male and female adult subjects.

Design: This was a randomized, single-dose, two-way, cross-over study under fasting conditions comparing equal doses of the test and reference products administered to 44 normal, healthy adults with 41completing the study [M 32; F 9. Age: 30 ± 10.3 (range 19 – 54)]. Blood samples were collected at pre-dose and at intervals over 24 hours after dosing each period. Subjects were confined at the clinical facility from at least 10 hours prior to dosing until after the 24 hour blood collection. The interval between doses was 7 days.

Following an overnight fast of at least 10 hours, ODT (Test A: 1 x 10 mg tablet) was administered (at 0 hour) by placing the tablet directly on the subjects tongue under direct observation. The subjects were instructed to close their mouth and let the tablet dissolve on their tongue. Once the subject believed the tablet had completely dissolved, the clinical staff performed a mouth check to confirm that the tablet had completely dissolved. Should the tablet not have completely dissolved, the subject re-closed their mouth and the clinic staff checked the mouth every 15 seconds until such time as the tablet completely dissolved. Time taken from dosing until the tablet has completely dissolved was recorded on the source document and CRFs. No water was provided with the tablet or allowed for one hour prior or post dose.

The reference Reglan® Tablet (Reference B: 1 x 10 mg tablet) was administered (at 0 hour) with 240 ml of room temperature tap water after an overnight fast of at least 10 hours. Subjects were instructed to swallow the tablet whole without chewing or biting. A mouth check was performed after dosing to ensure that the tablet was swallowed. Other than the water provided for dosing, no additional water was allowed for one hour prior or post dose.

Blood samples were collected at pre-dose (0), 5, 10, 15, 20, 30, 40, 50 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 hours post-dose.

Only samples from subjects who completed both periods of the study were analyzed. Concentrations of metoclopramide in plasma were determined using a fully validated analytical method.

Any subject who experienced emesis within 4 hours of dosing (based on two times the expected Tmax of around 1-2 hours) was dropped from the study and their samples were not sent for analysis.

Confidence intervals (90%) were constructed for the treatment ratios (test to reference) of both parameters using the log-transformed data and the two one-sided t tests procedure. Equivalence was concluded if the confidence intervals for the three log-transformed (Ln) parameters (AUC_{0-t}, AUC_{0-inf}, and Cmax) are within the 0.8000 to 1.2500 limits.

Analytical Method Validation: A method for determining metoclopramide in human plasma has been validated using an API 3000 LC/MS/MS system with detection in the range 0.5000 to 200.0 ng/mL. The interface used with the API 3000 LC/MS/MS was a Turbo Ionspray®. The analyte was quantitated using a protein precipitation extraction procedure. Each 200 µL aliquot of standard and QC sample was mixed with (b) (4) of internal standard working solution (b) (4) After vortexing and centrifuging, 0.80 mL of dilution solution was added to an autoinjector vial. Following the transfer of 200 µL supernatant to the vial and vortexing, 5.00 µL was injected onto a LC/MS/MS system. The validation parameters are as follows:

LLOQ (ng/mL)	0.50
ULOQ (ng/mL)	200.0
Standard Curve Concentrations (ng/mL)	0.5 – 200.0
QC concentrations (ng/mL)	1.5, 15.0 and 150.0
QC Intraday precision range (%)	1.8 – 6.4%
QC Intraday accuracy range (%)	100 – 106%
QC Interday precision range (%)	2.4 – 5.1%
QC Interday accuracy range (%)	101 – 102%

Results:

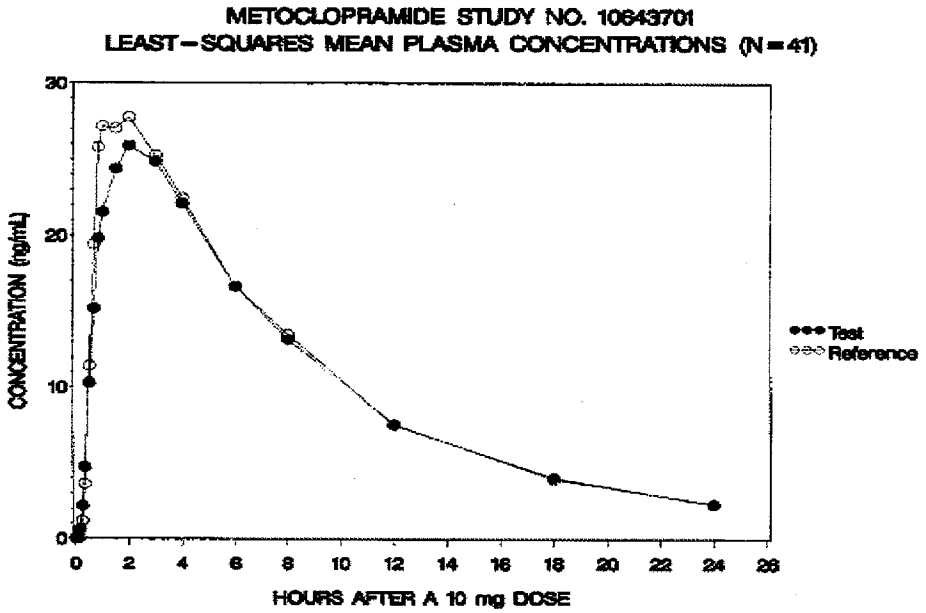
***In-vivo* disintegration time on the tongue:** Mean (± SD; N = 41) *in-vivo* disintegration time was 91 (± 164.83) seconds with median value of 45 seconds and range between 10 - 825 seconds. 90% (N=37) of the subjects had a disintegration time of 120 seconds or less and 73% (N = 30) of the subjects had a disintegration time of 60 seconds or less. The following table shows the values which are longer than 2 minutes:

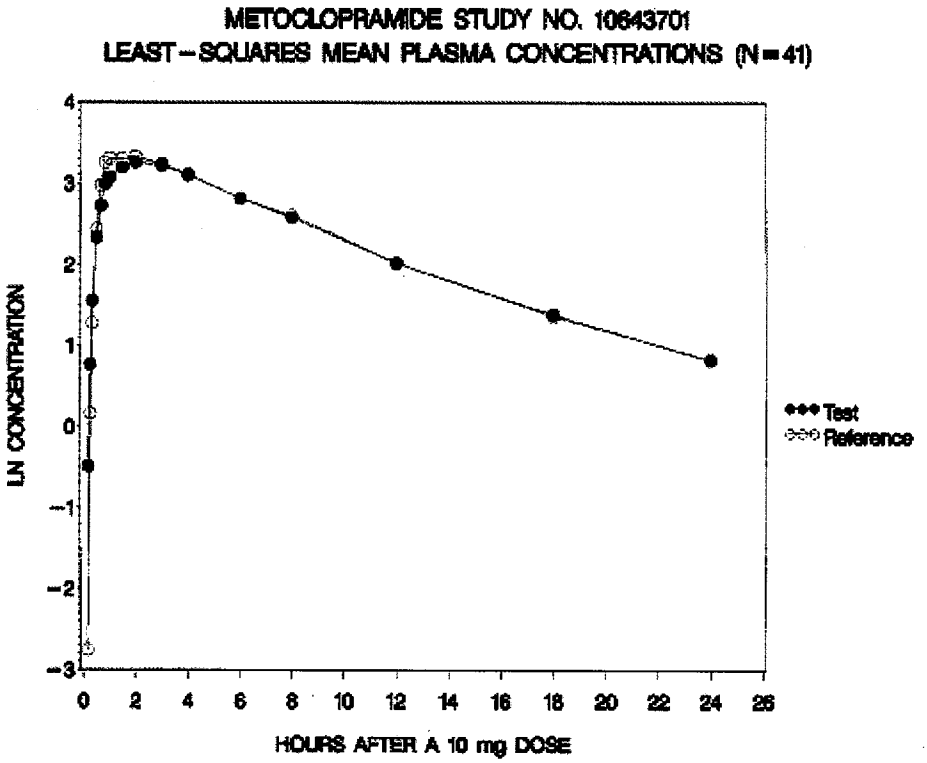
Subject	Disintegration time (secs)	Disintegration time (mins)

(b) (4)

Pharmacokinetcs:

The time-concentration profiles of test and reference in normal and log scales are presented below:





The test to reference ratios and corresponding 90% confidence intervals for metoclopramide are given in the following table:

Parameter	Least Squares Means [1]		Test/Ref. Ratio [2]	90% Confidence Interval [3]	
	Test A	Reference B		Lower	Upper
AUC 0-t (ng-hr/ml)	245.69	253.58	0.9689	0.9392	0.9987
AUC 0-inf (ng-hr/ml)	267.55	276.11	0.9690	0.9345	1.0035
Cmax (ng/ml)	27.90	30.33	0.9199	0.8765	0.9633
Kel (1/hour)	0.112	0.114	0.9809		
Elimhalf (hour)	6.38	6.30	1.0129		
Ln-Transformed Data					
AUC 0-t (ng-hr/ml)	238.04	244.60	0.9732	0.9456	1.0016
AUC 0-inf (ng-hr/ml)	258.30	264.71	0.9758	0.9447	1.0079
Cmax (ng/ml)	27.02	29.48	0.9165	0.8769	0.9579

Tmax (hour)	**Median**
Test A	2.00
Reference B	1.50

AUC 0-t / AUC 0-inf ratio [4]	
Test A	0.9183
Reference B	0.9184

1 Least squares geometric means for ln-transformed data.
2 Test/Ref. Ratio calculated as Test mean divided by Reference mean.
3 Confidence interval on the ratio.
4 AUC 0-t / AUC 0-inf ratio calculated as AUC 0-t mean divided by AUC 0-inf mean.

When log transformed, the test to reference ratio and the 90% confidence intervals for the major pharmacokinetic parameters [area under the plasma concentration curve (AUC0-t and AUC0-inf) and the peak plasma concentration (Cmax)] for metoclopramide were 0.9732 (0.9456 – 1.0016), 0.9758 (0.9447 – 1.0079), and 0.9165 (0.8769 – 0.9579), respectively.

Conclusion: Based on the statistical analysis of metoclopramide, Wilmington Pharmaceuticals, LLC's METZOLV® ODT 10 mg tablets are bioequivalent to REGLAN® (metoclopramide) Tablets 10 mg (Schwarz Pharma, Inc.) under fasted conditions.

Comment:

1. *One of the purposes of developing ODT is patient compliance, especially for pediatric, geriatric and psychiatric patients. The main focus of an ODT should be that it will disintegrate/dissolve on the tongue without liquid very quickly thereby greatly reducing the chances of spitting out the medication. The in-vivo disintegration data in this study is alarming in this regard as 12% (5/41) had disintegration time above 2 minutes and especially as high as 13.75minutes. In this reviewer's opinion, 12% is a significant number and as it appears, METZOLV® ODT defeats the purpose of an ODT. It should rather be taken by mouth with liquid like a conventional tablet.*

2. *The reviewer's analysis of BE data between the METZOLV® ODT 10 mg and REGLAN® Tablet 10 mg formulations are in agreement with the sponsor's result.*

NDA: 22-246/Study 10743701 **Study Dates: Jul '07 – Aug '07**

The Effect of Food on the Bioavailability of Metoclopramide 10 mg Orally Disintegrating Tablets (Wilmington Pharmaceuticals) and on its Relative Bioavailability with REGLAN® (metoclopramide) 10 mg Tablets (Schwarz Pharma).

Objective: The purpose of this study was to evaluate the relative bioavailability of the test formulation of metoclopramide orally disintegrating 10 mg tablets following a high fat breakfast compared to when the tablet was given under fasted conditions in healthy, male and female adult subjects. Additionally, the relative bioavailability of the test product was compared to that of the reference product when each was given with food.

Methodology: This randomized, single-dose, three-treatment, three-period, crossover study was conducted to compare two formulations of 10 mg metoclopramide tablets, under fasting and fed conditions. The study was conducted with 30 (28 subjects completing at least two periods of the study) healthy adults in accordance with protocol 10743701. In each study period, a single metoclopramide 10 mg tablet was administered to all subjects. Subjects received the test product METZOLV® ODT in one study period following an overnight fast of at least 10.5 hours (Test A) and in a second period following the FDA standardized breakfast preceded by an overnight fast of at least 10 hours (Test B). In a third period, subjects received the reference product REGLAN® (metoclopramide) USP 10 mg Tablets (Schwarz Pharma, Inc.) following the FDA standardized breakfast preceded by an overnight fast of at least 10 hours (Reference C).

Test A:	Metoclopramide Orally Disintegrating 10 mg tablets (Wilmington Pharmaceuticals, LLC) administered after an overnight fast
Test B:	Metoclopramide Orally Disintegrating 10 mg tablets (Wilmington Pharmaceuticals, LLC) administered after a standardized high fat breakfast
Reference C:	REGLAN® (metoclopramide) tablets 10 mg (Schwarz Pharma) administered after a standardized high fat breakfast

The order of administration was according to the dosing randomization schedule. There was a 7-day interval between treatments.

In both periods of the study with METZOLV® ODT , designated personnel administered the test product, I x 10 mg tablet (at 0 hour) by placing the tablet directly on the subjects tongue under direct observation. Each subject was instructed to close mouth and let the tablet dissolve on the tongue. Once the subject believed the tablet completely dissolved, the clinic staff member performed a mouth check to confirm that the tablet completely dissolved. The time taken from dosing until the tablet has completely dissolved was recorded on the source documentation and CRFs. No fluids other than the milk provided with the high fat breakfast was be provided with the tablet or allowed for one hour prior or post dose.

For dosing with the reference formulation, designated (b) (4) personnel administered the dose, 1 x 10 mg tablet (at 0 hour) with 240 ml of room temperature tap water immediately following a standardized high fat breakfast. Subjects were instructed to swallow the tablet whole without chewing or biting. A mouth check was performed after dosing to ensure that the tablet was swallowed. Other than the water provided for dosing, no additional water was allowed for one hour prior or post dose.

Blood samples were collected at pre-dose (0), 10 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 16 and 24 hours post-dose.

Results:

***In-vivo* disintegration time on the tongue:**

Mean (± SD; N = 41) *in-vivo* disintegration time was 66 (± 33.43) seconds with a median value of 59 seconds and range between 19 - 157 seconds. 91% (N=50) of the subjects had a disintegration time of 120 seconds or less and 53% (N = 29) of the subjects had a disintegration time of 60 seconds or less.

The following table shows the values which are longer than 2 minutes:

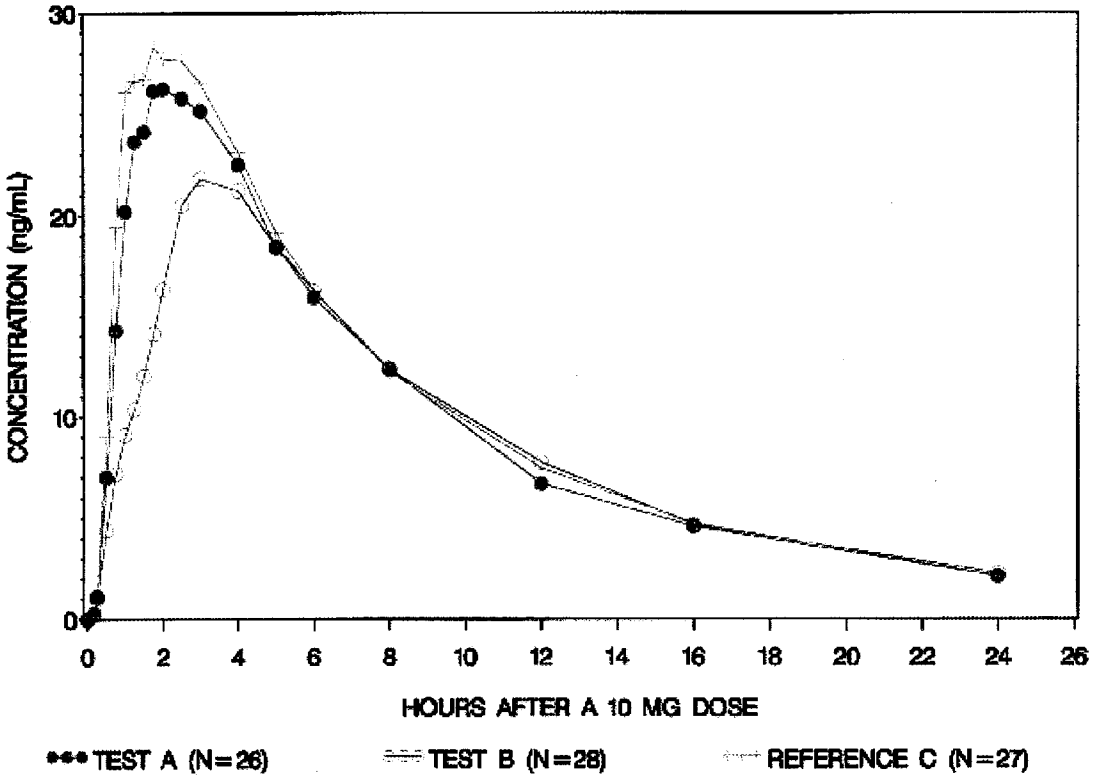
Subject	Disintegration time (secs)	Disintegration time (mins)

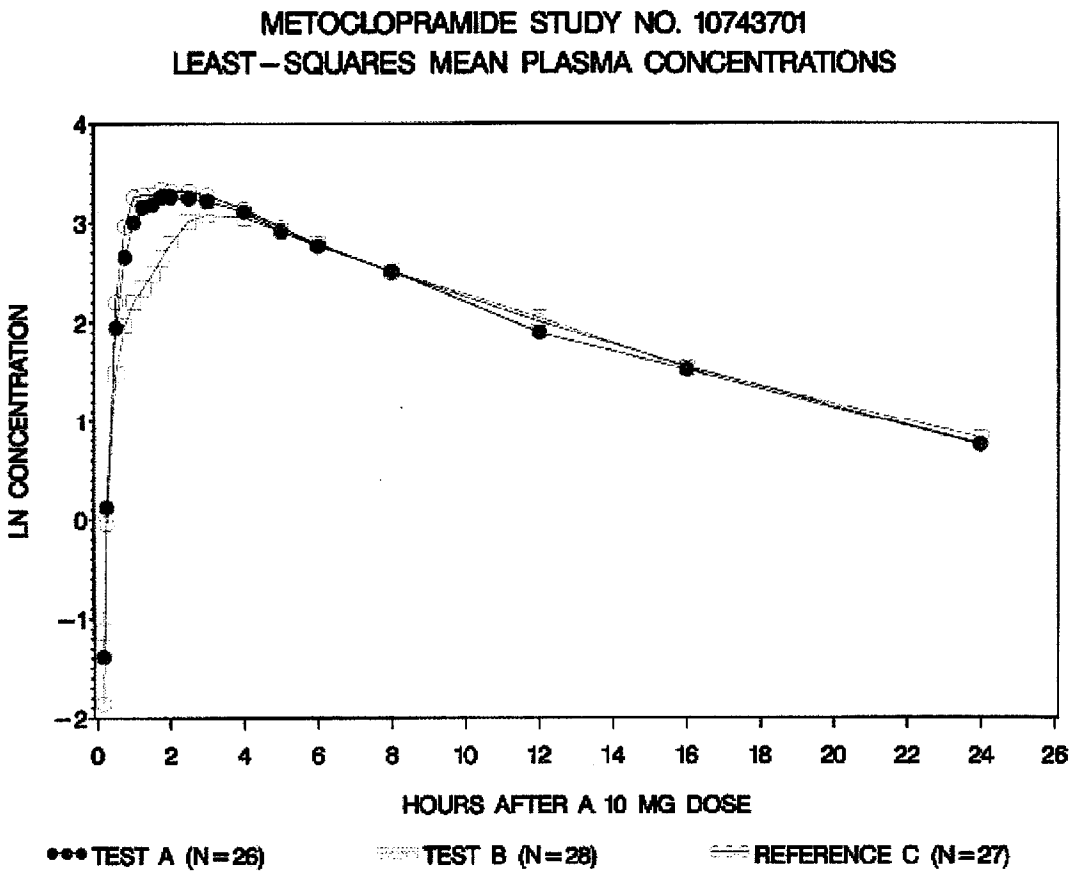
(b) (4)

Pharmacokinetcs:

The time-concentration profiles of test and reference in normal and log scales are presented below:

METOCLOPRAMIDE STUDY NO. 10743701
LEAST-SQUARES MEAN PLASMA CONCENTRATIONS





The test to reference ratios and corresponding 90% confidence intervals for metoclopramide are given in the following table:

Least Squares Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Untransformed Data

Parameter	Test B (Fed)	Test A (Fasted)	Ratio	CI
AUC0-t (ng•hr/ml)	206.29	226.10	0.9124	0.8587 – 0.9661
AUC0-inf (ng•hr/ml)	234.32	245.78	0.9534	0.9044– 1.0024
Cmax (ng/ml)	22.73	27.33	0.8317	0.7535 – 0.9099
Tmax (hr)	3.305	1.889	—	—
Kel (1/hr)	0.115	0.116	0.9861	0.9393 – 1.0329
Elimhalf (hr)	6.35	6.16	1.0316	0.9693 – 1.0939

Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data

Parameter	Test B (Fed)	Test A (Fasted)	Ratio	CI*	Intra-Subject %CV
AUC0-t (ng•hr/ml)	196.22	215.81	0.9092	0.8644 – 0.9564	11.3503
AUC0-inf (ng•hr/ml)	217.99	232.87	0.9361	0.8892 – 0.9855	11.1646
Cmax (ng/ml)	21.98	26.35	0.8340	0.7751 – 0.8974	17.7770

Least Squares Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Untransformed Data

Parameter	Test B (Fed)	Reference C (Fed)	Ratio	CI
AUC0-t (ng•hr/ml)	216.41	246.80	0.8769	0.8313 – 0.9224
AUC0-inf (ng•hr/ml)	245.66	268.43	0.9152	0.8742 – 0.9561
Cmax (ng/ml)	23.67	31.29	0.7564	0.6919 – 0.8209
Tmax (hr)	3.216	1.890	—	—
Kel (1/hr)	0.114	0.112	1.0182	0.9709 – 1.0654
Elimhalf (hr)	6.44	6.49	0.9921	0.9349 – 1.0494

Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data

Parameter	Test B (Fed)	Reference C (Fed)	Ratio	CI*	Intra-Subject %CV
AUC0-t (ng•hr/ml)	203.35	232.39	0.8750	0.8347 – 0.9173	9.3814
AUC0-inf (ng•hr/ml)	226.21	251.76	0.8985	0.8566 – 0.9425	8.8120
Cmax (ng/ml)	22.66	29.82	0.7598	0.7084 – 0.8148	14.7461

Reviewer's Analysis:

Study 107 Test B (Fed)/Test A (Fast) N = 28					
Parameter	Test B (Fed)	Ref A (Fast)	Ratio	90% CI Lower	90% CI Upper
AUC0-t	203.7954	223.0159	91.38	86.97	96.01
AUCinf	225.8384	240.4259	93.93	89.35	98.76
Cmax	22.8269	27.1247	84.16	78.31	90.44

Study 107 Test B (Fed)/Ref C (Fed) N= 28					
Parameter	Test B (Fed)	Ref C (Fed/Reglan)	Ratio	90% CI Lower	90% CI Upper
AUC0-t	203.7954	234.3612	86.96	82.83	91.29
AUCinf	225.8384	253.1587	89.21	84.93	93.71
Cmax	22.8269	30.2197	75.54	70.37	81.08

Conclusion: The overall oral bioavailability as evaluated using $LnAUC_{0\text{-}t}$, $LnAUC_{0\text{-}inf}$ demonstrated that total exposure (as measured by AUC) are same with or without food. However, peak plasma concentrations (Cmax) were slightly reduced (by about 17%) when the test product was taken following the high fat breakfast. This slight difference is not considered to be clinically relevant for this product. Again, in the secondary analysis, the overall bioavailability (LnAUC0-t and LnAUC0-inf) of Wilmington Pharmaceuticals, LLC's metoclopramide orally disintegrating 10 mg tablet compared to REGLAN® (metoclopramide) USP 10 mg Tablets (Schwarz Pharma, Inc.), was equivalent when both were taken in the fed state in terms of AUC. However, Cmax was approximately 24% lower for the test product compared to the reference product when both were taken following a high fat meal. It should be notted that the labeling for REGLAN® (metoclopramide) USP 10 mg Tablets (Schwarz Pharma, Inc.) recommends that these tablets be taken approximately 30 minutes prior to eating.

Comments:

1. *There is little difference between the Sponsor's and reviewer's analysis of PK data. But the difference is very small and did not make in difference in the outcome or conclusion of the study.*

2. *The in-vivo disintegration data in this study showed that 9% (5/55) had disintegration time above 2 minutes which is a concern.*

4.3 Filing Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-246	Brand Name	Reglan ODT
OCP Division (I, II, III)	III	Generic Name	Metoclopramide
Medical Division	180	Drug Class	Antiemetic
OCP Reviewer	Tapash K. Ghosh	Indication(s)	GERD and Gastroparesis
OCP Team Leader	Sue-Chih Lee	Dosage Form	Orally Disintegrating Tablet
		Dosing Regimen	prn
Date of Submission	2/07/2008	Route of Administration	Oral
Estimated Due Date of OCP Review	9/30/2008	Sponsor	Wilmington
PDUFA Due Date	11/30/2008	Priority Classification	3S
Division Due Date	10/30/2008		

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) -				
eers-				
single dose:	X	3		
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			
replicate design; single / multi dose:				
Food-drug interaction studies:	X			
Dissolution:				
(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		3	2	

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 Chlopramide ODT bioequivalent to IR Reglan tablet?** **What is the food effect?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Tapash Ghosh**	
Secondary reviewer Signature and Date	**Sue-Chih Lee**	

CC: NDA XX-XXX, HFD-XXX(CSO), HFD-8XX(TL, DD, DDD)

CC: NDA 22- 246, HFD-850, HFD-880 (TL, DD, DDD),

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tapash Ghosh
11/3/2008 04:00:22 PM
BIOPHARMACEUTICS

Sue Chih Lee
11/3/2008 05:32:54 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: Kristina Estes			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 6/18/09	NDA No.: 22-246 Serial No.:		DATE OF DOCUMENT	3/10/09
NAME OF DRUG **METOZOLV ODT (metoclopramide orally disintegrating tablet)**	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	3/11/09

NAME OF THE SPONSOR: Wilmington Pharmaceuticals

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

- ☐ PRE-IND
- ☐ ANIMAL to HUMAN SCALING
- ☐ IN-VITRO METABOLISM
- ☐ PROTOCOL
- ☐ PHASE II PROTOCOL
- PHASE III PROTOCOL
- DOSING REGIMEN CONSULT
- ☐ PK/PD- POPPK ISSUES
- ☐ PHASE IV RELATED
- ☐ DISSOLUTION/IN-VITRO RELEASE
- ☐ BIOAVAILABILITY STUDIES
- ☐ IN-VIVO WAIVER REQUEST
- ☐ SUPAC RELATED
- ☐ CMC RELATED
- ☐ PROGRESS REPORT
- ☐ SCIENTIFIC INVESTIGATIONS
- ☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)
- ☐ FINAL PRINTED LABELING
- ☒ **LABELING REVISION**
- ☐ CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ ANNUAL REPORTS
- ☐ FAX SUBMISSION
- ☐ OTHER *(SPECIFY BELOW)*: [ ]

REVIEW ACTION

- ☐ NAI (No action indicated)
- ☒ E-mail comments to: Project Manager
- ☐Medical☐Chemist☐Pharm-Tox
- ☐Micro☐Pharmacometrics☒Others
- (Check as appropriate and attach e-mail)
- ☐ Oral communication with Name: [ ]
- ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]
- ☒ Formal Review/Memo (attached)
- ☐ See comments below
- ☐ See submission cover letter
- ☐ OTHER *(SPECIFY BELOW)*: [ ]

REVIEW COMMENT(S)

☒ **NEED BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

BACKGROUND: The sponsor has submitted revised labeling in response to a Complete Response issued February 26th, 2009 detailing several safety concerns relevant to all metclopramide products. This product is also the first metoclopramide product to be submitted under the PLR format. The previous submission [a 505(b)(2) for an ODT utilizing Reglan Tablets as the RLD] was acceptable from a clinical pharmacology perspective, provided that agreement could be reached regarding a description of the disintegration time in the label.

RECOMMENDATION: We have reached agreement with the sponsor regarding the clinical pharmacology labeling issues. See Appendix below.

MMENTS: The following comments have been communicated to the sponsor and have been agreed upon.

Revised description of the disintegration time under Dosage and Administration and the Pharmacokinetics sections. [redacted] (b) (4) 3. Relocation of the pediatric PK data from section 12.3 (Pharmacokinetics) to section 8.4 (Pediatric Use). 4. [redacted] (b) (4).	
SIGNATURE OF REVIEWER: _KEE____ **SIGNATURE OF TEAM LEADER: ___**	Date _____ Date _____
CC.: HFD # []; TL: []	**Project Manager:_ Date:**

Appendix

NDA 22-246
Metozolv (metoclopramide orally disintegrating tablets) 5 mg & 10 mg
Labeling Supplement
Wilmington Pharmaceuticals

Background
Metoclopramide is a dopamine D2 receptor antagonist used in the treatment of a variety of GI disorders including prevention of nausea and vomiting and gastroparesis. An orally disintegrating tablet (Reglan ODT) was approved but not marketed and this sponsor has submitted a 505(b)(2) application for a similar ODT with Reglan tablets (oral tablets, not the ODT formulation) as the RLD. The 505(b)(2) application was reviewed by DCP and found to be acceptable provided that agreement could be reached regarding the language in the proposed package insert. The primary labeling issue from DCP was how best to describe the disintegration time for this product given the wide range observed in the clinical trials. In addition, both DGP and OSE agreed that a boxed warning, REMS, and Medication Guide would be necessary given the risk of irreversible drug-induced movement disorders. Therefore, a complete response was issued pending the resolution of these concerns.

The following sections of the proposed METOZOLV label contain material relevant to clinical pharmacology for which we (or the sponsor) recommend changes:

- Section 2, DOSAGE AND ADMINISTRATION
- Section 5.6, Congestive Heart Failure and Ventricular Arrhythmia
- Section 8.4, Pediatric Use
- Section 8.6, Other Special Populations
- Section 12.3, Pharmacokinetics

Section 2 (DOSAGE AND ADMINISTRATION)

Sponsor's Original Proposed Language
DOSAGE & ADMINISTRATION

(b) (4)

Clinical Pharmacology Recommendation
2. DOSAGE AND ADMINISTRATION

Take on an empty stomach at least 30 minutes before eating since food can decrease the peak concentrations of drug in the bloodstream and/or the time it takes to achieve the maximum drug level in the bloodstream*[see Clinical Pharmacology (12.3)]*. (b) (4)

Instructions for Safe Handling

Since the tablet absorbs moisture rapidly, only remove each dose from the packaging just prior to taking. Handle the tablet with dry hands and place on the tongue. If the tablet should break or crumble while

handling, discard and remove a new tablet.

(b) (4), Metozolv ODT (b) (4) disintegrates on the tongue in approximately one minute (with a range of 10 seconds to 14 minutes). (b) (4) (b) (4) METOZOLV ODT is designed to be taken without liquid; however, the effect on the pharmacokinetics of taking Metozolv ODT with liquid is unknown.

Reviewer's Comment

- Previously, the Division had proposed to insert "… varied widely (10 seconds to 14 minutes…) regarding the in vivo disintegration times; however, the sponsor suggests "… was approximately one minute…" instead. The label for Reglan ODT states "The tablet typically disintegrates in about one and one-half minutes." The Reglan ODT label does not describe the mean, SD, %CV, or median of the disintegration time, unlike the proposed label for Metozolv. The sponsor is not trying to suggest that the tablet will dissolve "rapidly" or "in seconds"; therefore, <u>an average or approximate time for disintegration is acceptable</u>. Furthermore, the SD, %CV, and median time for disintegration will be described in section 12.3 (pharmacokinetics).
- The food-effect statement is vague and may be interpreted as minimizing the absorption concerns.

Section 5.6, Congestive Heart Failure and Ventricular Arrhythmia

Sponsor's Original Proposed Language

(b) (4)

Clinical Pharmacology Recommendation

Since metoclopramide produces a transient increase in plasma aldosterone, patients with cirrhosis or congestive heart failure may be at risk of developing fluid retention and volume overload. If these side effects occur at any time in any patients during metoclopramide therapy, the drug should be discontinued.

(b) (4)

Reviewer's Comments

- (b) (4)

(b) (4)

- Cardiovascular adverse events are listed in Section 6.2, Post-Marketing Experience.

Section 8.4, Pediatric Use

The sponsor did include pediatric PK data (the working was identical to the label for the RLD); however, the placement of the information was not consistent with the new PLR format. Therefore, the pediatric PK data has been removed from Section 12.3 (Pharmacokinetics) and placed in Section 8.4. In addition, the two paragraphs which described the PK of *intravenous* metoclopramide were deleted as they do not apply to this *oral* product.

Section 8.6, Other Special Populations

Sponsor's Original Proposed Language

(b) (4)

Clinical Pharmacology Recommendation

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.

Since metoclopramide is excreted principally through the kidneys, therapy should be initiated at approximately one-half the recommended dose in those patients whose creatinine clearance is below 40 mL/min. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate. Metoclopramide has been safely used in patients with advanced liver disease whose renal function was normal.

(b) (4)

(b) (4)

Reviewer's Comments

- (b) (4)

Section 12.3 Pharmacokinetics

Sponsor's Original Proposed Language

(b) (4)

Clinical Pharmacology Recommendation

The in-*vivo* disintegration time (time reported between placing the tablet on the tongue and it completely disintegrated into fine particles) (b) (4) was approximately one minute (with a range of 10 seconds to 14 minutes). In the two clinical trials (N = 96) with a mean ± SD being 76.8 ± 110.6 seconds (b) (4) and a median of 53.5 seconds.

Reviewer's Comments

- The disintegration time is not a standard PK measure; therefore, including the coefficient of variation of this measurement is unlikely to be meaningful to heathcare practitioners. Providing the approximate disintegration time along with the range observed in clinical trials is sufficient to characterize the likely behavior of the drug in practice.
- This paragraph is not meant to be a duplicate of the information found in the DOSAGE AND ADMINISTRATION section; therefore, some more detailed information was provided to include the mean disintegration time and the SD.

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/s/

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