CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022524Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-524	Submission Date(s): 05/04/10
Submission Type; Code	Complete Response Resubmission, 505(b)(2)
Brand Name	Zuplenz Oral Soluble Film
Generic Name	Ondansetron
Reviewers	Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology Products
Sponsor	Par Pharmaceuticals, Inc.
Formulation; Strengths; Regimen	Oral Soluble Film 8 mg and 4 mg • HEC CINV: 24 mg given successively as three 8 mg oral soluble film administered 30 minutes before the start of single-day highly emetogenic chemotherapy • MEC CINV: o For adults and pediatric patient 12 years of age and older, one 8-mg oral soluble film given twice a day o For the 4 through 11 years old, one 4-mg oral soluble film given 3 times a day. • Radiotherapy: one 8-mg oral soluble film given 3 times a day • PONV: 16 mg given successively as two 8 mg oral soluble film 1 hour before induction of anesthesia
Proposed Indication	• Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin > 50 mg/m^2 • Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy • Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen • Prevention of postoperative nausea and/or vomiting (PONV).

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1 Executive Summary and Recommendation

1.1 Recommendation

The division of clinical pharmacology 3 has reviewed the resubmitted application and has found it acceptable from a clinical pharmacology standpoint provided that a mutual agreement can be reached on the labeling languages.

1.2 PMR

The sponsor has committed to conduct the following clinical pharmacology-related pediatric studies as PMR under PREA.

Study 1: Deferred pediatric study for the prevention of nausea and vomiting in pediatric cancer patients ages 4 to <17 years receiving highly emetogenic chemotherapy (HEC).

> A PK and safety study to characterize the pharmacokinetics of Zuplenz (ondansetron) oral soluble film in pediatric patients ages 4 to <17 years receiving HEC.

Study 3: Deferred pediatric study for the prevention of postoperative nausea and vomiting (PONV) in pediatric surgical patients ages 0 to <17 years.

> A PK and safety study to characterize the pharmacokinetics of Zuplenz (ondansetron) oral soluble film in pediatric surgical patients ages 0 to <17 years. An age-appropriate formulation must be developed for younger pediatric patients.

1.3 Regulatory Background

Submitted is resubmission of NDA 22-524 for Ondansetron Oral Soluble Film in response to Complete Response (CR) letter that was issued on 02/05/10. Original NDA application for Ondansetron Oral Soluble Film 8 mg and 4 mg was submitted on 04/07/09 under 505(b)(2) provision using Zofran (Ondansetron) Orally Disintegrating Table 8 mg as reference product. The sponsor relied on the Agency's findings of safety and efficacy of the reference product for Zuplenz Oral Soluble Film based on the bioequivalence established between Zuplenz Oral Soluble Film 8 mg and Zofran 8 mg. Due to travel advisory for the region, FDA was not able to conduct a DSI inspection of the clinical and analytical sites for the bioequivalence study "An Open-Label Randomized, Single Oral Dose, Two-Way Crossover Bioequivalence Study To Compare Ondansetron Orally Dissolving Film Strip (ODFS) 8 mg with Zofran Orally Disintegrating Tablets [ODT® (containing Ondansetron 8 mg)] in 48 Healthy, Adult, Human Study Participants Under Fasting Conditions" (study # 01905/08-09) as of 02/05/10. Therefore, the sponsor was issued CR letter on 02/05/10 that also enclosed Agency's proposed revision of the product label.

1.4 Submission contents:

- DSI inspection report and sponsor's response to deficiencies
- Sponsor's revised label

1.5 DSI Inspection Report

An inspection of the clinical and analytical sites for the bioequivalence study "An Open-Label Randomized, Single Oral Dose, Two-Way Crossover Bioequivalence Study To Compare Ondansetron Orally Dissolving Film Strip (ODFS) 8 mg with Zofran Orally Disintegrating Tablets [ODT® (containing Ondansetron 8 mg)] in 48 Healthy, Adult, Human Study Participants Under Fasting Conditions" was completed on April 22, 2010 by the Division of Scientific and Investigations (DSI). The clinical portion of study was conducted at (b) (4) , and the analytical portion was conducted at (b) (4) Since (b) (4) ceased operations prior to this inspection, inspections of the clinical and analytical portions were conducted at (b) (4)

Following the inspection, the DSI had following comments and conclusion:

- The firm failed to conduct adequate incurred sample reproducibility (ISR) assessment.
- The firm's SOP for ISR is insufficient.
- The firm failed to fully report and discuss all data generated during assay validation.
- The firm failed to follow the protocol.

Conclusion: Following DSI's evaluation of the inspectional findings and the firm's response, DSI recommends that the inspected clinical and analytical portions be accepted for review (see appendix).

We agree with the recommendation of DSI from clinical pharmacology standpoint.

2 Detailed Labeling Recommendations

The agency's proposed revisions to the product label were enclosed with the Complete Response letter dated on 02/05/10. The sponsor has accepted most of the agency's proposed revisions and it also proposed some new revisions in this resubmission. Reviewer's recommended addition is shown with an underline and deletion is shown with ~~strikethrough line~~.

7 DRUG INTERACTIONS

7.1 Apomorphine

Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with ondansetron is contraindicated.

7.3 Tramadol

Although there are no data on pharmacokinetic drug interaction between ondansetron and tramadol (b) (4) data from 2 small studies indicate that concomitant use of ondansetron may (b) (4) result in reduced analgesic activity of tramadol, leading to an increased dose in patient controlled administration of tramadol.

7.5 Antacids

Bioavailability of ondansetron is unaffected by antacids

12 CLINICAL PHARMACOLOGY

12. 3 Pharmacokinetics

Absorption

Ondansetron is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. After a single dose of ZUPLENZ (ondansetron) oral soluble film 8 mg under fasting conditions (n=46), the peak plasma concentrations were achieved in 1.3 hours and the mean elimination half-life was 4.6 hours in healthy subjects. The mean (±S.D.) C_{max} and AUC were 37.28 (±14.9) ng/mL and 225 (±88.1) ng·h/mL, respectively. In the same study, mean ondansetron C_{max} and AUC following administration of 8 mg ZUPLENZ oral soluble film were (b) (4) comparable to those after 8 mg ondansetron ODT (orally disintegrating tablet). The systemic exposure after administration of ZUPLENZ oral soluble film 8 mg with or without water was found to be comparable.

Food Effect

When administered with a high fat meal, (b) (4) 8 mg ZUPLENZ (ondansetron) oral soluble film's mean time to peak plasma concentration (t_{max}) was delayed by approximately 1 hour and its AUC remained similar compared to that of under fasted stated. (b) (4)

3 Appendix

3.1 DSI Inspection Report:

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 17, 2010

TO: Donna J. Griebel, M.D.
Director
Division of Gastroenterology Products (DGP)

FROM: John A. Kadavil, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. _____
Acting Team Leader (Bioequivalence)
Division of Scientific Investigations (DSI)

SUBJECT: Review of EIR Covering NDA 22-524, Zuplenz (Ondansetron) Orally Dissolving Film Strip 8 mg, Sponsored by Monosol Rx

The attached Appendix for the 3.1 DSI Inspection Report (3 pages following this page) dated May 17, 2010 has been withheld as a duplicate copy. This May 17, 2010, DSI Inspection Report can be located in the Other Reviews section of this NDA approval package.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22524	ORIG-1	PAR PHARMACEUTICAL	ZUPLENZ (ONDASETRON) ORALLY-DISSOLVING F

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

/s/

DILARA JAPPAR
06/29/2010

SUE CHIH H LEE
06/30/2010

EDWARD D BASHAW
07/01/2010

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	22-524	Submission Date(s)	04/07/2009; 5/01/09; 08/10/09; 09/22/09; 10/19/09; 11/04/09; 1/11/10
Brand Name		Zuplenz Oral Soluble Film (Pending)	
Generic Name		Ondansetron	
Reviewer		Insook Kim, Ph.D.	
Team Leader		Sue-Chih Lee, Ph.D.	
OCP Division		Division of Clinical Pharmacology 3	
OND Division		Division of Gastroenterology Products	
Sponsor		Par Pharmaceuticals, Inc.	
Submission Type;		Original	505 (b)(2)
Formulation; Strengths; Regimen		Oral Soluble Film 8 mg and 4 mg • HEC CINV: 24 mg given successively as three 8 mg oral soluble film administered 30 minutes before the start of single-day highly emetogenic chemotherapy • MEC CINV: One 8-mg oral soluble film given twice a day for 12 years and older • For the 4 through 11 years old, one 4-mg oral soluble film given 3 times a day prior to 30 minutes before the start of chemo, with subsequent doses 4 and 8 hours after the first dose. One 4-mg film should be administered 3 times a day for 1 to 2 days after completion of chemotherapy. • Radiotherapy: one 8-mg oral soluble film given 3 times a day • PONV: 16 mg given successively as two 8 mg oral soluble film 1 hour before induction of anesthesia	
Indication		• Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin > 50 mg/m^2 • Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy • Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen • Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis in not recommended for patients in whom there is little	

	expectation that nausea and/or vomiting must be avoided postoperatively, Tradename is recommended even where the incidence of postoperative nausea and/or vomiting is low.

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1 Executive Summary

Submitted is a New Drug Application for Ondansteron Oral Soluble Film 8 mg and 4 mg under 505(b)(2) provision using Zofran (Ondansetron) Orally Disintegrating Table 8 mg as reference product. The sponsor is relying on the Agency's findings of safety and efficacy of the reference product for Zuplenz Oral Soluble Film based on the bioequivalence established between Zuplenz Oral Soluble Film 8 mg and Zofran 8 mg. Originally, the sponsor proposed Zuplenz Oral Soluble Film as Zuplenz® Orally Dissolving Film Strip. However, the Agency determined during the review cycle that the name for the formulation should be "Oral Soluble Film". As such, the formulation is referred as Oral Soluble Film in this review. Note that an optional intra-divisional level of Clinical Pharmacology Briefing was held to discuss this NDA on December 17, 2009.

As of February 1, 2009, the DSI inspection has not been carried out due to a travel advisory for the region. The travel advisory was issued as a result of civil and political unrest that have risen in the area. Due to this unresolved issue, the Clinical Division has planned on taking a Complete Response (CR) action.

1.1 Recommendations

The division of clinical pharmacology 3 has reviewed the submitted application and has found it acceptable from a clinical pharmacology standpoint provided that the pending DSI inspection on the clinical study site and the bioanalytical analysis site for the pivotal BE study will be satisfactory and a mutual agreement can be reached on the labeling languages.

1.2 Phase IV Commitments

Not at this time.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

In support of the current application, the sponsor submitted five final study reports, including one fasting bioequivalence study (study 01905/08-09), a fed bioequivalence study (study 01906/08-09), a relative bioavailability study among Tradename administered with or without water and Zofran ODT 8 mg administered without water (Study 04795/08-09) and two pilot BE studies under fasting and fed conditions; study 10221/06-07 and 10222/06-07, respectively. In this review, the pilot BE studies were not evaluated in details. The sponsor also evaluated the time to dissolve the Oral Soluble Film and the reference product in vivo during each BA/BE study. No additional clinical trials for efficacy and safety of Ondansetron Oral Soluble Film were conducted. The sponsor requested a biowaiver for Ondansetron Oral Soluble Film 4 mg and conducted in vitro dissolution study in comparison to Zofran ODT 4 mg. According to the CMC reviewer, a biowaiver is granted for the lower strength of Ondansetron Oral Soluble Film 4 mg (Please, see CMC review for more details).

The Ondansetron Oral Soluble Film 8 mg is bioequivalent to Zofran 8 mg administered under the fasting condition.

The relative bioavailability between the Tradename and the reference product under fasting condition was evaluated in study 01905/08-09 titled "An open-label randomized, single oral dose, two way crossover bioequivalence study to compare ondansetron Orally Dissolving FilmStrip (ODFS) 8mg with Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] in 48 healthy, adult, human study participants under fasting conditions." Both products were dissolved on the tongue and swallowed with saliva followed by 240 ml water intake. The fasting bioequivalence study is considered a pivotal BE study and DSI inspection is pending for the clinical site which is in (b) (4) as of December 1, 2009.

After a single dose administration, the peak plasma concentration was reached around 1 hour for both products and the mean elimination half-life was about 4-5 hours (Table 1). The mean Cmax and AUC after Tradename was about 8-9% lower than those after administration of the reference product, Zofran 8 mg. The 90% confidence interval associated with the least squares geometric mean ratio of Cmax and AUC fell within the bioequivalence criteria 80-125% (Table 2). As such the bioequivalence between single dose Tradename 8 mg and Zofran 8 mg was established under fasting condition.

Table 1. Mean (SD) PK parameters of Ondansetron after administration of 8 mg Tradename (test) and Zofran (reference) 8 mg under fasting condition (n=46)

PK Parameter (Units)	Ondansetron	
	Treatment A (Test)	Treatment B (Reference)
C_{max} (ng/mL)	37.282 (14.9177)	41.108 (17.2442)
AUC_{0-t} (ng.hr/mL)	216.269 (83.2883)	239.463 (100.0745)
$AUC_{0-\infty}$ (ng.hr/mL)	225.032 (88.2551)	250.673 (107.9654)
T_{max} (Hour)	1.33 (1.00, 4.00)	1.17 (0.67, 3.00)
$t_{1/2}$ (Hour)	4.673 (0.8491)	4.786 (1.1740)
Kel (1/hr)	0.154 (0.0356)	0.156 (0.0550)

*For T_{max} Median (Min, Max) are presented.

Table 2. Summary of bioequivalence analysis between Tradename and Zofran (reference) product under fasting condition

PK Parameter	Least Squares Geometric Means of Treatment		Comparison	Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test (A)	Reference (B)				
C_{max} (ng/mL)	34.5723	37.9520	A vs B	91.09	18.35	(85.46, 97.10)
AUC_{0-t} (ng.hr/mL)	201.3261	218.2403	A vs B	92.25	12.67	(88.26, 96.42)
$AUC_{0-\infty}$ (ng.hr/mL)	209.0275	227.8907	A vs B	91.72	12.70	(87.74, 95.88)

***Reviewer's comments**: In a few subjects, multiple plasma peaks within 5 hours post-dose were observed regardless of products indicating variability in Ondansetron absorption.*

The Ondansetron Oral Soluble Film 8 mg is bioequivalent to Zofran 8 mg administered under fed condition.

The relative bioavailability between the Tradename and the reference product under fed condition was in study 01906/08-09 titled "An open-label randomized, single oral dose, two way crossover bioequivalence study to compare ondansetron Orally Dissolving FilmStrip (ODFS) 8mg with Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] in 48 healthy, adult, human study participants under fed conditions..

Following 30 min after a high fat meal, the test and reference product was dissolved on the tongue and swallowed with saliva followed by 240 ml water intake.

Under fed condition, the mean time to peak plasma concentration was delayed by an hour. In a cross-study comparison with study 01905/08-09, under fed condition, after single administration of Tradename, the mean Cmax was decreased from 34 to 26 ng/ml while AUC were comparable to that under fasting condition (Table 3).

Table 3. Mean (SD) PK parameters after a single dose of Tradename (test) and Zofran (reference) under fed condition (n=45)

Study Ref. No.	Formulation	C_{max} (ng/mL)	T_{max} hr	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	$t_{1/2}$ (hr)	K_{el} (hr^{-1})
01906/08-09	Test	26.017 (36.64)	2.67 (1.00-4.02)	201.020 (46.09)	213.713 (47.85)	5.089 (19.24)	0.142 (22.18)
	Reference	25.694 (33.84)	2.67 (0.67-6.00)	212.120 (45.47)	225.891 (49.08)	5.149 (19.17)	0.139 (19.35)

Note: For C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$ and K_{el} Arithmetic Mean and %CV values were reported
For T_{max}, Median and Range values were reported

The mean Cmax was comparable between Tradename and the reference product and mean AUC was about 7% lower for Tradename than the reference product. The 90% confidence interval associated with the least squares geometric mean ratio of Cmax and AUC fell within the bioequivalence criteria 80-125% (Table 4). As such the bioequivalence between single dose Tradename 8 mg and Zofran 8 mg was established under fed condition.

Table 4. Summary of bioequivalence analysis between Tradename and the reference product under fed condition

PK Parameter	Least Squares Geometric Means of Treatment:		Comparison	Ratio (%)	90% CI of Ratio
	Test (A)	Reference (B)			
C_{max} (ng/mL)	24.4389	24.3941	A Vs B	100.18	(94.68, 106.00)
AUC_{0-t} (ng.hr/mL)	182.5014	195.0514	A Vs B	93.57	(88.97, 98.40)
$AUC_{0-\infty}$ (ng.hr/mL)	193.1032	205.9382	A Vs B	93.77	(89.15, 98.63)

Ondansetron Oral Soluble Film 8 mg can be administered with or without water

The effect of water intake following Ondansetron Oral Soluble Film administration was evaluated in study 04795/08-09 titled "An open-label randomized, single oral dose, three way crossover comparative water effect bioavailability study to compare ondansetron Orally Dissolving Filmstrip (ODFS) 8mg with and without water with Zofran Orally Dissolving Tablets (ODT®) without water in 18 adult, healthy human study participants under fasting conditions."

There was no significant difference in PK parameters for Ondansetron regardless of administration methods of Ondansetron Oral Soluble Film (Table 5). In addition, the

ratio of Cmax and AUC between Ondansetron Oral Soluble Film administered either with or without water to Zofran ODT administered without water were 97-106% and the associated 90% CI fell within 80-125% (Table 6).

Table 5. Summary of Pharmacokinetic Parameters of Ondansetron after administration of Tradename without water (treatment A), with water (treatment B) and reference product without water (treatment C) (n=17)

Summary Statistics	Ondansetron					
	C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	T_{max} (Hour)	$t_{1/2}$ (Hour)	K_{el} (1/hr)
Treatment A (Test):						
Mean (SD)*	40.866 (13.3089)	290.687 (106.5203)	311.349 (119.7910)	2.00	5.567 (1.0863)	0.129 (0.0243)
GM	38.817	272.635	290.245	1.82	5.470	0.127
(Min, Max)	(18.924, 73.982)	(148.555, 485.124)	(152.739, 536.952)	(1.00, 2.67)	(4.141, 7.445)	(0.093, 0.167)
%CV	32.57	36.64	38.47	25.72	19.51	18.84
Treatment B (Test):						
Mean (SD)*	42.843 (15.9103)	291.069 (99.5911)	310.394 (112.7499)	1.67	5.738 (0.9205)	0.124 (0.0208)
GM	40.017	274.616	291.045	1.58	5.667	0.122
(Min, Max)	(19.653, 78.167)	(142.465, 470.851)	(148.953, 525.460)	(0.67, 3.00)	(4.337, 7.068)	(0.098, 0.160)
%CV	37.14	34.22	36.32	38.97	16.04	16.75
Treatment C (Reference):						
Mean (SD)*	39.382 (12.3572)	285.457 (105.3048)	306.497 (121.8256)	1.67	5.460 (1.3789)	0.135 (0.0357)
GM	37.521	267.497	284.842	2.02	5.295	0.131
(Min, Max)	(21.221, 61.008)	(144.937, 484.983)	(151.443, 562.754)	(1.67, 3.00)	(3.130, 7.886)	(0.088, 0.221)
%CV	31.38	36.89	39.75	24.99	25.26	26.44

A: Oral Soluble Film administered without water
B: Oral Soluble Film administered with water
C: Reference Product administered without water

Table 6. Ratio of Least Squares Geometric Means of Treatment associated 90% CI of ratio

Treatment Comparison	Cmax (n=17)	AUCt (n=17)	AUCinf (n=17)
A vs. C	103.38 (93.57, 114.21)	102.33 96.50, 108.51)	102.38 (96.31, 108.82)
B vs. C	106.28 (96.20, 117.43)	102.43 (96.60, 108.62)	101.93 (95.90, 108.35)
A vs. B	97.26 (88.03, 107.46)	99.90 (94.21, 105.93)	100.44 (94.49, 106.76)

A: Oral Soluble Film administered without water
B: Oral Soluble Film administered with water
C: Reference Product administered without water

In vivo Oral Disintegration/Dissolution

The time for Oral Soluble Film and Orally Dissolving Tablet to dissolve on the tongue was measured during clinical trials. The test and reference products were opened and removed from the package with dry hands and immediately placed on the tongue where it was dissolved and was then swallowed with saliva. Clinical personnel ensured that the products were removed from the pouch in its entirety.

The median time take to dissolve Ondansetron Oral Soluble Film on the tongue was 3-4 seconds longer than the median oral disintegration time of Zofran ODT. Both products dissolved within 21 seconds (Table 7).

Table 7. Time (in seconds) taken for dissolution of drug on the tongue

Study 01905/08-09

Statistic	ODFS	ODT
Mean	10.94	7.93
SD	3.47	3.46
Median	10.58	7.26
Min	4.79	3.00
Max	20.69	19.50
N	46.00	48.00

Study 01906/08-09

Statistic	ODFS	ODT
Mean	10.45	6.71
SD	2.82	1.98
Median	10.28	6.53
Min	4.19	3.46
Max	17.47	12.23
N	46.00	47.00

Note that ODFS refers Oral Soluble Film

Reviewer's comments: *For the prevention of highly emetogenic chemotherapy (HEC) induced nausea and vomiting, 24 mg of Ondansetron should be administered. For Oral Soluble Film 8 mg, three Films should be administered successively after complete dissolution of a previous Film. If administered as recommended, it will take less than 1.5 min and this time taken for administration is not expected to have effects on safety and efficacy of the product.*

The systemic exposure of Ondansetron was higher in female subjects than male subjects after a single dose of Zuplenz Oral Soluble Film

In the pivotal BE study, 85% of subjects enrolled were males while the higher systemic exposure of Ondansetron in female subjects than male subjects was previously noted (Zofran ODT label). When the data was analyzed by gender, mean AUC and Cmax were higher in females than in males regardless of the treatments. The variability of PK parameters was in general greater for male subjects except for Tmax regardless of treatment with %CV ranging 17-43% than for female subjects with %CV ranging 14-27%. Nonetheless, the mean Cmax and AUC in females after Zuplenz Oral Soluble Film was 25% and 20% higher than after Zofran ODT while mean Cmax and AUC in males were comparable (Table 8).

Reviewer's comments: *In this study, the ratio of mean Cmax and AUC of Tradename to reference product was 94% and 91.5%, respectively in male subjects and 79% and 83%, respectively in female subjects. It is unknown why the difference in mean Cmax and AUC between two products is greater in female subjects although the general trend of a higher systemic exposure in female is consistent. Because of a small number of female subjects i.e. n=7, a firm conclusion can not be drawn as to the bioequivalence of two products in female subjects.*

Table 8. Ondansetron Pharmacokinetic Parameters by Gender after Fasting Administration of 8 mg Ondansetron Oral Soluble Film (referred as ODFS) and 8 mg ZOFRAN ODT® (Study 01905/08-09)

Treatment	Gender		Weight (kg)	Cmax (ng/mL)	Tmax (hr)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Half Life (hr)
8 mg Ondansetron ODFS	Female	N	7	7	7	7	7	7
		Mean	56.7	49.1	1.67	307	323	5.39
		SD	3.77	9.23	0.67	54.7	61.4	0.741
		Min	51.0	36.9	1.00	243	251	4.85
		Median	57.0	47.1	1.33	295	306	5.02
		Max	61.0	67.2	3.00	404	432	6.70
		CV%	6.7	18.8	40.1	17.8	19.0	13.8
	Male	N	39	39	39	39	39	39
		Mean	62.0	35.2	1.70	200	207	4.54
		SD	7.47	14.8	0.74	77.1	80.8	0.810
		Min	50.0	15.2	1.00	81.9	84.8	2.27
		Median	62.0	30.9	1.33	180	186	4.56
		Max	80.0	73.1	4.00	395	409	6.53
		CV%	12.0	42.2	43.6	38.6	39.0	17.8
8 mg ZOFRAN ODT®	Female	N	7	7	7	7	7	7
		Mean	56.7	61.8	1.48	366	389	5.63
		SD	3.77	13.5	0.81	81.1	102	1.49
		Min	51.0	38.3	0.67	289	297	4.28
		Median	57.0	63.7	1.00	341	349	5.18
		Max	61.0	80.1	3.00	531	601	8.57
		CV%	6.7	21.8	55.0	22.2	26.3	26.4
	Male	N	39	39	39	39	39	39
		Mean	62.0	37.4	1.44	217	226	4.63
		SD	7.47	15.2	0.55	85.8	89.4	1.06
		Min	50.0	15.3	0.67	56.3	58.0	1.73
		Median	62.0	33.7	1.33	201	208	4.60
		Max	80.0	86.4	2.67	448	465	7.67
		CV%	12.0	40.6	38.3	39.6	39.6	22.9

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Ondansetron is a selective serotonin receptor antagonist (5-HT_3) and was approved as an anti-emetic agent. Ondansetron is indicated for prevention of chemotherapy-induced

nausea and vomiting, radiotherapy-induced nausea and vomiting and postoperative nausea and vomiting.

The reference product for the current application is Zofran Orally Disintegrating Tablet 8 mg (NDA 20-781). Zofran ODT 4 mg and 8 mg were approved based on the in vivo bioequivalence to the Zofran tablet 4 mg and 8 mg (NDA 20-103) in January 27, 1999 (Table 9). Ondansetron is also available as oral solution and an injectable for intravenous administration.

Table 9. Geometric Mean Ratio of Cmax and AUC of Zofran ODT 8 mg to Zofran tablet 8 mg (Adapted from Clinical Pharmacology and Biopharmaceutics Review of NDA 20-781 dated July 29, 2998 by Dr. Alfredo R. Sancho).

Ratio (90% CI)	Test 8 mg w/o	Test 8mg w/ water
Cmax	1.03 (0.98-1.09)	0.96 (0.91-1.01)
$AUC_{0-\infty}$	1.03 (0.99-1.08)	1.01 (0.97-1.06)

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Ondansetron Oral Soluble Film is a white opaque film strip, imprinted with "4 MG" or "8 MG", to designate the product strength, in black ink. The OSF product is designed to deliver ondansetron base perorally to the GI tract for systemic absorption. Ondansetron OSF is available in the following strengths/dimensions. This is the first application to use Oral Soluble Film formulation for drug delivery.

Ondansetron (8 mg ondansetron) OSF contains 8 mg ondansetron base; dimensions 22 mm x 32 mm • Ondansetron (4 mg ondansetron) OSF contains 4 mg ondansetron base; dimensions 22 mm x 16 mm. The high strength 8 mg ODFS is exactly twice the length and therefore has exactly twice the surface area of the 4 mg ODFS. The high strength ondansetron 8 mg ODFS is also twice as heavy (at 56.8 mg per strip) compared to the ondansetron 4 mg ODFS (at 28.4 mg per strip) – (b) (4)

Both strengths of ondansetron OSF utilize the same formulation – (b) (4) the same composition and method of manufacture. The high strength 8mg and low strength 4 mg products are therefore dose proportional differing in piece weight (Table 10). The biowaiver is granted for the low strength 4 mg product (please, see CMC review for more details.)

The Oral Soluble Film is designed to dissolve on tongue and the median time for a complete dissolution on the tongue was about 10 seconds with a range of 4 to 21 seconds (Please see

Table 7). The median in vivo dissolution time on the tongue reference product Zofran Orally Disintegrating Tablet was about 7 seconds with a range of 3 to 20 seconds.

Table 10. Quantitative Formula of Ondansetron Oral Soluble Film

Formulation strength	High Strength Ondansetron ODFS (8mg ondansetron)		Low Strength Ondansetron ODFS (4mg ondansetron)	
Component	WT %	mg/strip	WT %	mg/strip
Ondansetron Base	(b) (4)	8.00	(b) (4)	4.00
Hydroxypropyl methylcellulose (b) (4)				
Polyethylene Oxide (b) (4)				
Erythritol (b) (4)				
Peppermint Flavor (b) (4)				
Calcium Carbonate (b) (4)				
Sucralose				
Colloidal Silicon Dioxide (b) (4)				
Titanium Dioxide				
Sodium Bicarbonate				
Monoammonium Glycyrrhizinate (b) (4)				
Xanthan Gum (b) (4)				
Butylated Hydroxytoluene (b) (4)				
Total	100.00%	60[1]	100.00%	30

[1] Represents the theoretical film strip weight. The actual weight adjusted for loss of flavor during processing is (b) (4)

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Ondansetron is a selective serotonin receptor antagonist (5-HT_3) and was approved as an anti-emetic agent. The sponsor proposes to rely on the indications for Zofran ODT under a 505(b)(2) provision as below:

- Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin > 50 mg/m^2
- Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy
- Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen
- Prevention of postoperative nausea and/or vomiting. As with other anti-emetics, routine prophylaxis in not recommended for patients in whom there is little expectation that nausea and/or vomiting must be avoided postoperatively,

Tradename is recommended even where the incidence of postoperative nausea and/or vomiting is low.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Ondansetron Oral Soluble Film 4 mg and 8 mg is to be administered orally by dissolving on the tongue and swallowed by saliva with or without water intake afterward.

2.2 General Biopharmaceutics

2.2.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the reference product?

The relative bioavailability of Tradename Oral Soluble Film 8 mg to the reference product 8 mg is 92% under fasting condition (Please, see Table 2).

***Reviewer's comments**: All the pharmacokinetic studies were conducted in* (b) (4) *in support of current application. As such the participated subjects had Indian ethnic background. Although the study population is not reflective of the general U.S. population in terms of ethnicity, it does not raise a concern for this application. When compared with the PK parameters for the reference product in* (b) (4)*, PK parameters obtained for this application in India were reasonably comparable although mean Cmax and AUC in this application were higher than obtained in* (b) (4) *(Table 11).*

Table 11. PK parameters for the reference products

	Zofran ODT with 240 ml water (n=46)	Zofran ODT with 150 mg water (b) (4) study 517/410 (n=24)
Cmax (ng/ml)	41.11 ± 17.24 (41.94%)	33.7 ± 13.13 (38.96%)
AUCt (ng·h/ml)	239.46 ± 100.07 (41.79%)	N/A
AUCi (ng·h/ml)	250.67 ± 107.97 (43.07%)	206± 34.2 (16.6%)
Tmax (h)	1.17 (0.67, 3)	2.02 ± 0.77
T1/2 (h)	4.79 ± 1.17 (24.43%)	3.8 ± 0.97 (25.53%)

The rate and extent of absorption after single dose of Ondansetron Oral Soluble Film 8 mg was compared with that after single dose of the reference product Zofran ODT 8 mg under fasting condition and under fed condition. Two administration methods i.e. administration with or without water were compared (Table 12). The Pharmacokinetic parameters were calculated by using Non-compartmental model. Please, see attached individual study synopses for more information and reviewer's comments.

Table 12. Summary list of pharmacokinetic studies

Table Study No. Investigator	Study Objective(s)	Study Design	No. Subjects Age Range (Mean)[1]	Treatment, Dose [Lot or Product ID]
Pivotal Bioequivalence Studies				
01905/08-09 (b) (4)	Determine the bioequivalence of ondansetron orally dissolving Film Strip compared to the marketed reference product (Zofran Orally Distintegrating Tablets) in fasting healthy volunteers.	Open label, Randomized, Single Dose; Crossover; Oral Administration; Fasting State	Enrolled: 48 (41M/7F) Males: 18-40 (25.0) Females: 27-38 (33.4) Completed: 46	Reference Product Zofran ODT® (Containing Ondansetron 8 mg) Orally Disintegrating Tablets 1 x 8 mg [Lot #511932-8211]
				Test Product: Ondansetron ODFS 8mg film 1 x 8 mg [Lot # E08DD201-158]
01906/08-09 (b) (4)	Determine the bioequivalence of ondansetron orally dissolving Film Strip compared to the marketed reference product (Zofran Orally Distintegrating Tablets) in fed healthy volunteers.	Open label, Randomized, Single Dose; Crossover; Oral Administration; Fed State	Enrolled: 48 (36M/12F) Males: 18-41 (25.5) Females: 20-39 (30.3) Completed: 45	Reference Product Zofran ODT® (Containing Ondansetron 8 mg) Orally Disintegrating Tablets 1 x 8 mg [Lot #511932-8211]
				Test Product: Ondansetron ODFS 8mg film 1 x 8 mg [Lot # E08DD201-158]

Table 12 (continued). Summary list of pharmacokinetic studies

Table Study No. Investigator	Study Objective(s)	Study Design	No. Subjects Age Range (Mean)	Treatment, Dose [Lot or Product ID]
Bioavailability Study				
04795/08-09 (b) (4)	Determine the bioequivalence of ondansetron orally dissolving Film Strip compared to the marketed reference product (Zofran Orally Distintegrating Tablets) in fasting healthy volunteers with and without water.	Open label, Randomized, Single Dose; Crossover; Oral Administration; Fasting State; with and without water	Enrolled: 18 (14M/4F) Males: 19-39 (25.9) Females: 33-39 (35.0) Completed: 17	Reference Product Zofran ODT® (Containing Ondansetron 8 mg) Orally Disintegrating Tablets 1 x 8 mg [Lot #511932-8211]
				Test Product: Ondansetron ODFS 8mg film 1 x 8 mg [Lot # E08DD201-158]
Pilot Bioequivalence Studies				
10221/06-07 (b) (4)	Determine the bioequivalence of ondansetron orally dissolving Film Strip compared to the marketed reference product (Zofran Orally Distintegrating Tablets) in fasting healthy volunteers.	Open label, Randomized, Single Dose; 2 Period Crossover; Oral Administration; Fasting State; both products administered with water.	Enrolled: 12 (12M/0F) Males: 20-41 (25.3) Completed: 12	Reference Product Zofran ODT® (Containing Ondansetron 8 mg) Orally Disintegrating Tablets 1 x 8 mg [Lot #511933]
				Test Product: Ondansetron ODFS 8mg film 1 x 8 mg [Master Lot No: G07DD2-01 Lot No: G07DD201-215]
10222/06-07 (b) (4)	Determine the bioequivalence of ondansetron orally dissolving Film Strip compared to the marketed reference product (Zofran Orally Distintegrating Tablets) in fed healthy volunteers.	Open label, Randomized, Single Dose; 2 Period Crossover; Oral Administration; Fed State; both products administered with water.	Enrolled: 12 (12M/0F) Males: 18-36 (25.5) Completed: 12	Reference Product Zofran ODT® (Containing Ondansetron 8 mg) Orally Disintegrating Tablets 1 x 8 mg [Lot #511933]
				Test Product: Ondansetron ODFS 8mg film 1 x 8 mg [Master Lot No: G07DD2-01 Lot No: G07DD201-215]

2.3 Analytical Section

2.3.1. How is Ondansetron measured in the plasma in bioequivalence studies? What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What is the accuracy, precision and selectivity at these limits?

Ondansetron in human plasma was analyzed by a LC-MS/MS method with (b) (4) as internal standard. The bioanalytical assay method was adequately validated with acceptable accuracy and precision (Table 13). The linearity was established from 0.51 ng/ml to 91.503 ng/ml. The accuracy and precision at the lower limit of quantitation (LLOQ) was 105.10% and 6.28%, respectively.

Table 13. Summary of Bioanalytical Assay Validation Results

Information Requested	Data
Report Location	Study Report No.: 01905/08-09 & 01906/08-09; Section-16.4
Analyte	Ondansetron
Internal standard (IS)	(b) (4)
Method description	Refer Method Validation report No. 23/MVR/ONDANSETRON/038 Page No. 13 of 48 Analytical method: LC-MS/MS
Limit of quantitation	0.510 ng/mL
Average recovery of drug (%)	76.72 %
Average recovery of IS (%)	65.28 %
Standard curve concentrations (ng/mL)	0.510, 1.020, 3.051, 10.170, 20.334, 40.668, 61.002 and 91.503ng/mL.
QC concentrations (ng/mL)	LQC= 1.527ng/mL GMQC= 9.162ng/mL MQC= 50.900ng/mL HQC= 71.260ng/mL
QC Intra batch precision range (%)	LQC= 2.65% to 4.15% GMQC= 1.29% to 3.40% MQC= 1.42% to 2.06% HQC= 1.59% to 3.63%
QC Intra batch accuracy range (%)	LQC= 90.77% to 97.18% GMQC= 91.60% to 95.58% MQC= 88.71% to 89.89% HQC= 89.72% to 91.72%
QC Inter batch precision range (%)	LQC= 4.46% GMQC= 2.98% MQC= 1.81% HQC= 2.58%
QC Inter batch accuracy range (%)	LQC= 93.19% GMQC= 93.46% MQC= 89.21% HQC= 90.76%
Bench-top stability (hrs)	16.00 hours at ambient temperature (% Stability of LQC=93.84% & HQC=93.11%)
(b) (4) stability (hrs)	21.00 hours at ambient temperature (% Stability of LQC=92.01% & HQC=89.93%)

Table 13 (continued). Summary of Bioanalytical Assay Validation Results

(b) (4) stability (hrs)	21.00 hours at ambient temperature (% Stability of LQC=89.33% & HQC=92.57%)
In injector stability (hrs)	26.00 hours at 10°C temperature (% Stability of LQC=89.52% & HQC=91.77%)
Stock stability (days)	59 days @ 2 to 8°C (% Stability of LQC=101.55% & HQC=100.98%) ISTD=99.96%
Freeze-thaw stability (cycles)	Three cycles (Accuracy range of LQC= 96.33% & HQC= 95.04%)
Long-term storage stability (days)	56 days @ -20°C (% Stability of LQC= 96.01% & HQC= 95.19%)
Dilution integrity	1.7 times of CC8 concentration (152.697 ng/mL) diluted in 1:5 (% Accuracy= 98.53% & %CV= 3.02%)
Selectivity	No interfering peaks noted in blank plasma samples

3 Detailed Labeling Recommendations

Most of the section 12. Clinical Pharmacology information is borrowed from the approved label of the reference product. The proposed label is in PLR format while the label of the reference product is not. The sponsor added Bioequivalence subsection under 12.3 Pharmacokinetics to describe findings of bioequivalence studies. In this section, review of new information in the label is done. The format review will be deferred until labeling negotiation. Reviewer's recommended addition is shown with an underline and deletion is shown with ~~strikethrough line~~.

12 CLINICAL PHARMACOLOGY

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2. Individual Study Synopsis

Study 01905/08-09

Name of Sponsor: MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	**Name of Finished Product:** Ondansetron ODFS 8mg film.	**Name of Active Ingredient:** Ondansetron

Title of Study:
An open-label randomized, single oral dose, two way crossover bioequivalence study to compare ondansetron Orally Dissolving FilmStrip (ODFS) 8mg (Manufactured by MonoSol Rx, USA) with Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] (Manufactured by Cardinal Health Blagrove, Swindon, Wiltshire, UK, SN58RU for Glaxo SmithKline, Research Triangle Park, NC 27709, Made in England) in 48 healthy, adult, human study participants under fasting conditions.

Investigators: Principal Investigator: – Dr. Sudershan Vishwanath.
Medical Investigator: – Dr. B. Satish Kumar.

Study Centre: **Clinical facility**	**Bio-Analytical, Pharmacokinetic & Statistical facility:**
(b) (4)	(b) (4)

Publication (Reference):

1. Physicians' Desk Reference. 61st ed. Montvale, NJ: Thomson PDR; 2007. Zofran ODT ® (Ondansetron) Orally Disintegrating Tablets; p. 1639-1642.
2. Package insert/label for Zofran™ (Glaxo Smith Kline)
3. SOP No: 63/01: Randomization of subjects for allocation of treatment.
4. SOP No: 22/81/MAA: Receipt, Storage, Dispensing Retention and Dispatch of Investigational Products.
5. SOP No: 23/13: Repeat analysis of samples and re-integration of Chromatograms.
6. SOP No: 23/47: Incurred Samples Reanalysis

Phase of the Study: Bioequivalence Study.

Study Period:
Study Start Date: 16 Sep 2008 (Initial date of Volunteer Screening)
Study Completion Date: 26 Sep 2008 (Final date of Last Participant Study Exit)

Name of Sponsor: MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	Name of Finished Product: Ondansetron ODFS 8mg film.	Name of Active Ingredient: Ondansetron

Objectives:

- To assess the single dose bioequivalence of ondansetron ODFS 8mg (Manufactured by MonoSol Rx, USA) with Zofran ODT® (Containing Ondansetron 8 mg) (Manufactured by Cardinal Health Blagrove, Swindon, Wiltshire, UK, SN58RU for Glaxo SmithKline, Research Triangle Park, NC 27709, Made in England) in healthy, male and female adult, human study participants under fasting conditions.
- To monitor clinical status, adverse events, laboratory investigations and to assess relative safety and tolerance of ondansetron formulations under fasting conditions.

Methodology:

All study related procedures, restrictions, duration, dates and timings, information on the study formulation and confidentiality of participant data were explained clearly to the volunteers by clinical personnel at the time of obtaining informed consent. Volunteers who signed the consent form and showed their willingness to participate in the study were enrolled. Volunteers who satisfied the inclusion and exclusion criteria and found to be healthy on physical examination with laboratory investigation values within reference limits were considered eligible to be admitted into the study. Volunteers whose pre-study laboratory values were outside the reference range were allowed to participate, provided these values were determined to be clinically insignificant by Medical Investigator. The eligible volunteers reported to the study site on 17 Sep 2008 and 24 Sep 2008 for Period I and Period II, respectively, between 07:00 am to 05:00 pm.

Study participants and Study Activities:

Study participants were served dinner between 08:00 pm to 08:30 pm, to ensure minimum of 10 hours fasting prior to dosing in both the periods. Dosing was conducted as per the randomization schedule in each period under fasting conditions. A washout period of 07 days was observed between the two periods. Study restrictions with respect to fluid intake and physical activity were implemented throughout their stay in the Clinical Pharmacology Unit.

Blood samples were obtained as per protocol, centrifuged and plasma was separated. All plasma samples, meant for estimation of Ondansetron, were stored at temperature ranging between –17.3°C and –24.1°C (from the date of first sample collection until the last day of analysis).

Number of Study participants Planned:

The planned sample size was 48. Out of 48 participants enrolled for the study, 46 of them completed both clinical periods i.e. period 1 and period 2 of the study.

Number of Samples from Study participants Analyzed:

Plasma samples of 46 completed participants (Participants 1-48 except participants 04 & 09) were analyzed. Pharmacokinetic & Statistical analyses included a maximum of 46 study participants' data (see **Section 10.1** for details).

Name of Sponsor: MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	Name of Finished Product: Ondansetron ODFS 8mg film.	Name of Active Ingredient: Ondansetron

Main Criteria for Inclusion: Healthy adult study participants between 18-45 years (inclusive) of age who were willing to participate in the study by providing written and informed consent.

Investigational Products, Dose, Mode of Administration and Batch/Lot Number:

Test Product:	Reference Product:
Ondansetron ODFS 8mg film. Lot No.:E08DD201-158 Manufactured By: MonoSol Rx, LLC, USA .	Zofran ODT® (Containing Ondansetron 8 mg) Orally Disintegrating Tablets. Lot No.:511932-8211 Manufactured By: Cardinal Health Blagrove, Swindon, Wiltshire, UK, SN58RU. Manufactured For: Glaxo SmithKline, Research Triangle park, NC 27709.

The above two products were administered as following study treatments after an overnight fasting for at least 10 hours, in each study period:

Treatment (A): Single dose of Ondansetron ODFS 8 mg was orally administered, allowed to dissolve, swallowed with saliva, followed with 240 mL of drinking water at room temperature.

Treatment (B): Single dose of Zofran ODT® (Containing Ondansetron 8 mg) was orally administered, allowed to dissolve, swallowed with saliva, followed with 240 mL of drinking water at room temperature.

Duration of Treatment:
(from date of check in to last participant's study exit)
Period-I: 17 Sep 2008 to 19 Sep 2008
Period-II: 24 Sep 2008 to 26 Sep 2008

Bioanalytical Methods: Plasma samples were analyzed for ondansetron using a validated analytical method developed at (b) (4) Analysis was done under ultra violet (UV) filtered lighting conditions

Pharmacokinetic Blood Sampling: A total of 18 blood samples (4 mL each) were collected under golden yellow light (with UV filters) in each period.

Blood samples were collected as per the following schedule in each period:
The first blood sample was collected within 1 hour prior to drug administration (0.0 hour) and the others at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 15.0, 18.0 and 24.0 hours post dose.

Name of Sponsor: MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	Name of Finished Product: Ondansetron ODFS 8mg film.	Name of Active Ingredient: Ondansetron

Pharmacokinetic Analysis: Based on the plasma concentrations of Ondansetron, the following pharmacokinetic parameters were calculated by using "Non-compartmental model" for Treatments A and B: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, k_{el} and $t_{½}$. All pharmacokinetic analysis was carried out using WinNonlin Ent Version 4.1.

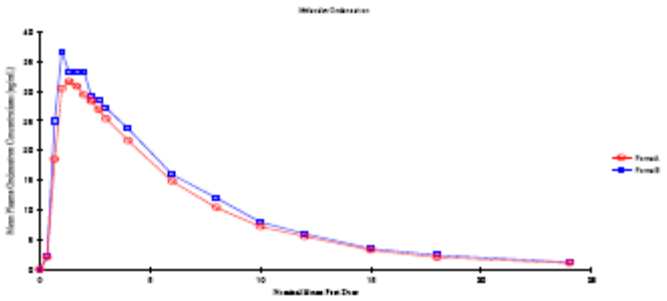
Safety Assessments: The safety assessments included monitoring of adverse events including adverse drug reactions, periodic physical examination, vital signs monitoring at regular pre-determined intervals and whenever appropriate. Pre study 12-lead ECG, Chest X-ray, Urinalysis and Serology were conducted for screening of volunteers. Pre study Hematology and Serum Chemistry assessments were done to select study participants with baseline values within reference ranges or clinically insignificant values if outside the reference range and post study these were repeated to determine any clinically significant abnormality. Urine Drug Screening was done at the time of check-in of both the study periods to identify study participants for any substance abuse. Urine pregnancy screen (for female volunteers only) was done at the time of check-in of both the study periods and at post study. A clinical assessment, which includes medical history, general and systemic examination was done at the pre-study screening and post study examination. These investigations were carried out for ensuring safety of study participants and scientific integrity of the study.

Descriptive Statistics: The descriptive statistics (such as N, mean, SD, minimum, maximum, median, %CV) were calculated for all the PK parameters for each test and reference treatments. Additionally geometric mean was calculated for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. For T_{max} median was reported as descriptive statistics.

Linear mixed effect model was used to assess the relative bioavailability of Treatment A (Test) versus Treatment B (Reference) for Ondansetron. The PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were natural log transformed before analysis. The model included terms for sequence, period and treatment as fixed effects and study participants nested within sequence as random effect. Within the framework of mixed effects model, least squares means (LSMeans) for Treatment A and B, the difference between LSMeans of test Treatment A versus reference Treatment B and the corresponding 90% CIs for the difference between LSmeans were calculated in natural log scale. The LSMeans, the LSMean differences, and the 90% CIs obtained in the natural log scale were exponentiated to obtain geometric means, the ratio estimates and the 90% CI of ratio estimates in the original scale. If the 90% CIs of the ratio estimates of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were all within 80.00 to 125.00% range for Ondansetron, then Treatment A was concluded as bioequivalent to Treatment B.

Name of Sponsor:	Name of Finished Product:	Name of Active Ingredient:
MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	Ondansetron ODFS 8mg film.	Ondansetron

Figure I: Mean Plasma Ondansetron Concentrations Vs Time Plot – Linear Scale



Pharmacokinetic Results:

Table 1 Mean (SD)* of Pharmacokinetic Parameters of Ondansetron

PK Parameter (Units)	Ondansetron	
	Treatment A (Test)	Treatment B (Reference)
C_{max} (ng/mL)	37.282 (14.9177)	41.108 (17.2442)
AUC_{0-t} (ng.hr/mL)	216.269 (83.2883)	239.463 (100.0745)
$AUC_{0-\infty}$ (ng.hr/mL)	225.032 (88.2551)	250.673 (107.9654)
T_{max} (Hour)	1.33 (1.00, 4.00)	1.17 (0.67, 3.00)
$t_{1/2}$ (Hour)	4.673 (0.8491)	4.786 (1.1740)
Kel (1/hr)	0.154 (0.0356)	0.156 (0.0550)

*For T_{max} Median (Min, Max) are presented.

NOTE: The above data is excerpted from Table 14.2.2-1 and 14.2.2-2, Section 14.2.

Statistical Results:

Table 2 Statistical Analysis Results for the Assessment of Bioequivalence Based on Pharmacokinetic Parameters of Ondansetron

PK Parameter	Least Squares Geometric Means of Treatment:		Comparison	Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test (A)	Reference (B)				
C_{max} (ng/mL)	34.5723	37.9520	A Vs B	91.09	18.35	(85.46, 97.10)
AUC_{0-t} (ng.hr/mL)	201.3261	218.2403	A Vs B	92.25	12.67	(88.26, 96.42)
$AUC_{0-\infty}$ (ng.hr/mL)	209.0275	227.8907	A Vs B	91.72	12.70	(87.74, 95.88)

NOTE: The above results are excerpted from Table 14.2.3-1, Section 14.2

The 90% CI for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within 80.00-125.00% range.

Name of Sponsor: MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	Name of Finished Product: Ondansetron ODFS 8mg film.	Name of Active Ingredient: Ondansetron

Safety Results:

In this study, test formulation, of ondansetron the study drug appeared to be comparably tolerated as that of reference, upon single-dose administration to healthy, adult, human study participants.

A total of 15 AEs in 13 study participants were reported.

Out of 15 AEs, 03 AEs were reported during the housing of period-I (i.e. Abdominal pain reported by participants 44 & 47, and Vomiting reported by participant 46) and the product received by them was treatment A (i.e. Test product). All of these were considered as mild in severity. Relationship wise, one AE i.e. vomiting was judged to be unrelated (participant 46): This AE was considered as unrelated as it has neither temporal relationship nor can it be ascribed to investigational product (Pharmacologically implausible) and 2 other AEs (abdominal pain)were considered as unlikely related to the study drug,

Another 12 AEs were reported during post clinical assessment (i.e. Eosinophil count increased for participants 4 & 18, AST increased for participant 13, Total bilirubin increased for participant 15, ALT increased for participants 20, 27, 31 & 36, Decreased platelet count for participant 37, lymphocyte count increased for participant 38, WBC count increased and upper respiratory tract infection for participant 47). All of these were graded as mild changes. Of these, one laboratory change was judged to be unrelated (i.e. WBC count in participant 47), 5 were judged to be unlikely related (participants 4, 18, 37, 38 & 47) and 6 were judged to be possibly related (participants 13, 15, 20, 27, 31 & 36) to the study drug by the investigator.

The outcomes of all cases (except laboratory changes and upper respiratory tract infection in participant 47) were resolved with no sequelae. The outcome of participant 47 with respect to laboratory changes and upper respiratory tract infection was unknown as the participant was lost on follow up. (See Appendix 16.2 entitled Subject Data Listings 16.2.7 Individual Subjects Adverse Events and Appendix 14.3 entitled Safety Summaries Table 14.3.1 Number of Distinct Subjects with Adverse Events and Table 14.3.3 Out of Range Laboratory Values).

Name of Sponsor: MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	Name of Finished Product: Ondansetron ODFS 8mg film.	Name of Active Ingredient: Ondansetron

Conclusion:

A single dose of Ondansetron ODFS 8mg was determined to be bioequivalent and equally tolerated to a single dose of Zofran ODT® (Containing Ondansetron 8 mg) (reference formulation) when both products were tested under fasting conditions in healthy, adult, human study participants.

The rate and extent of absorption parameters i.e. C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ under fasting condition were found to be similar for both reference (Zofran ODT®) and test treatment of Ondansetron.

The 90% CI of Ratio estimates of Ondansetron ODFS 8mg film versus Zofran ODT® (Containing Ondansetron 8 mg) Orally Disintegrating Tablets were [85.46, 97.10], [88.26, 96.42] and [87.74, 95.88] for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, respectively. All of these were within acceptable range of 80 to 125 % for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Thus based on these criteria bioequivalence is established in this study.

Overall, a single dose of Ondansetron Orally Dissolving FilmStrip (ODFS) 8mg (Manufactured by MonoSol Rx, USA) and a single dose of Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] (Manufactured by Cardinal Health Blagrove, Swindon, Wiltshire, UK, SN58RU for Glaxo SmithKline, Research Triangle Park, NC 27709, Made in England), when given under fasting condition seem to have been equally tolerated by both groups comprising of 46 healthy, adult human participants. Of 48 participants, two "study participants 04 & 09" were absent on period II admission day hence these participants were considered as incomplete cases not suitable for bioanalytical estimations.

Date of Final Report: 28 Jan 2009

Reviewer's comment: The reviewer repeated the PK parameter analysis and BE assessment and obtained the same results and conclusion. The number of subjects was determined based on the results from a pilot BE study with 12 subjects (study 10222/06-07). In the pilot BE study under fasting condition, the 90% CI for LSMean ratio of Cmax was (94,131.13) and the intrasubject variability for Cmax was 22.61%. In the pivotal BE study with 46 subjects, the intrasubject variability calculated for Cmax was 18.03%.

The pilot BE studies were conducted only in male subjects while the pivotal study was conducted with both male and female subjects. In the pilot BE study under fasting condition, the ratio of mean Cmax and AUC of Tradename to reference product was 108% and 104%, respectively. In this study, the ratio of mean Cmax and AUC of Tradename to reference product was 94% and 91.5%, respectively in male subjects and 79% and 83%, respectively in female subjects. Because of a small number of female subjects i.e. n=7, a firm conclusion can not be drawn as to the bioequivalence of two products in female subjects.

Study 01906/08-

Name of Sponsor: MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	**Name of Finished Product:** Ondansetron ODFS 8mg film.	**Name of Active Ingredient:** Ondansetron

Title of Study:
An open-label randomized, single oral dose, two way crossover bioequivalence study to compare ondansetron Orally Dissolving FilmStrip (ODFS) 8mg (Manufactured by MonoSol Rx, USA) with Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] (Manufactured by Cardinal Health Blagrove, Swindon, Wiltshire, UK, SN58RU for Glaxo SmithKline, Research Triangle Park, NC 27709, Made in England) in 48 healthy, adult, human study participants under fed conditions.

Investigators: Principal Investigator: – Dr. Sudershan Vishwanath.
Medical Investigator: – Dr. B. Kamalesh Kumar.

Study Centre: **Clinical facility** (b) (4)	**Bio-Analytical, Pharmacokinetic & Statistical facility:** (b) (4)

Publication (Reference):

1. Physicians' Desk Reference. 61st ed. Montvale, NJ: Thomson PDR; 2007. Zofran ODT ® (Ondansetron) Orally Disintegrating Tablets; p. 1639-1642.
2. Package insert/label for Zofran™ (Glaxo Smith Kline)
3. SOP No: 63/01: Randomization of subjects for allocation of treatment.
4. SOP No: 22/81/MAA: Receipt, Storage, Dispensing Retention and Dispatch of Investigational Products.
5. SOP No: 23/13: Repeat analysis of samples and re-integration of Chromatograms.
6. SOP No: 23/47: Incurred Samples Reanalysis

Phase of the Study: Bioequivalence Study.

Study Period:
Study Start Date: 06 Oct 2008 (Initial date of Volunteer Screening)
Study Completion Date: 24 Oct 2008 (Final date of Last Participant Study Exit)

09

Name of Sponsor: MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	Name of Finished Product: Ondansetron ODFS 8mg film.	Name of Active Ingredient: Ondansetron

Objectives:

- To assess the single dose bioequivalence of Ondansetron ODFS 8mg (Manufactured by MonoSol Rx, USA) with Zofran ODT® (Containing Ondansetron 8 mg) (Manufactured by Cardinal Health Blagrove, Swindon, Wiltshire, UK, SN58RU for Glaxo SmithKline, Research Triangle Park, NC 27709, Made in England) in healthy, male and female adult, human study participants under fed conditions.
- To monitor clinical status, adverse events, laboratory investigations and to assess relative safety and tolerance of ondansetron formulations under fed conditions.

Methodology:

All study related procedures, restrictions, duration, dates and timings, information on the study formulation and confidentiality of participant data were explained clearly to the volunteers by clinical personnel at the time of obtaining informed consent. Volunteers who signed the consent form and showed their willingness to participate in the study were enrolled. Volunteers who satisfied the inclusion and exclusion criteria and found to be healthy on physical examination with laboratory investigation values within reference limits were considered eligible to be admitted into the study. Volunteers whose pre-study laboratory values were outside the reference range were allowed to participate, provided these values were determined to be clinically insignificant by Medical Investigator. The eligible volunteers reported to the study site on 15 Oct 2008 and 22 Oct 2008 for Period I and Period II, respectively, between 07:00 am to 05:30 pm.

Study participants and Study Activities:

Study participants were served dinner between 09:00 pm to 09:30 pm, to ensure minimum of 10 hours fasting prior to dosing in both the periods. Dosing was conducted as per the randomization schedule in each period under fed conditions. A washout period of 07 days was observed between the two periods. Study restrictions with respect to fluid intake and physical activity were implemented throughout their stay in the Clinical Pharmacology Unit.

Blood samples were obtained as per protocol, centrifuged and plasma was separated. All plasma samples, meant for estimation of Ondansetron, were stored at temperature ranging between –16.6°C and –24.2°C (from the date of first sample collection until the last day of analysis).

Number of Study participants Planned:

The planned sample size was 48. Out of 48 participants enrolled for the study, only 45 of them completed both clinical periods i.e. period 1 and period 2 of the study.

Number of Samples from Study participants Analyzed:

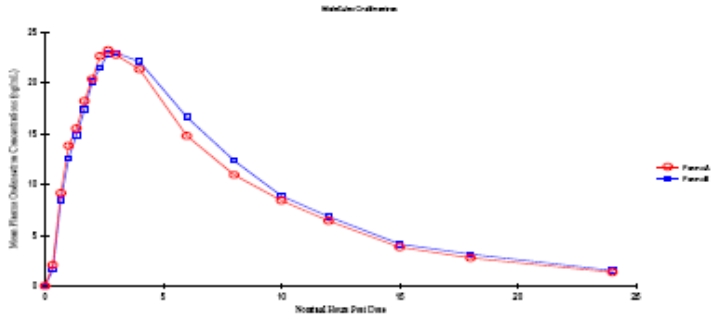
Plasma samples of 45 completed participants (Participants 1-48 except participants 24, 36 & 38) were analyzed. Pharmacokinetic & Statistical analyses included a maximum of 45 Study participants' data (see **Section 10.1** for details).

Name of Sponsor: MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	**Name of Finished Product:** Ondansetron ODFS 8mg film.	**Name of Active Ingredient:** Ondansetron
Main Criteria for Inclusion: Healthy adult Study participants between 18-45 years (inclusive) of age who were willing to participate in the study by providing written informed consent.		
Investigational Products, Dose, Mode of Administration and Batch/Lot Number:		
Test Product: Ondansetron ODFS 8mg film. Lot No.:E08DD201-158 Manufactured By: MonoSol Rx, LLC, USA .	**Reference Product:** Zofran ODT® (Containing Ondansetron 8 mg) Orally Disintegrating Tablets. Lot No.:511932-8211 Manufactured By: Cardinal Health Blagrove, Swindon, Wiltshire, UK, SN58RU. Manufactured For: Glaxo SmithKline, Research Triangle park, NC 27709.	
The above two products were administered as following study treatments. Both study treatments were administered after consumption of high fat breakfast which was served 30 minutes prior to the scheduled study medication. High fat breakfast was scheduled after observing an overnight fasting for at least 10 hours: **Treatment (A):** Single dose of Ondansetron ODFS 8 mg film (Manufactured by MonoSol Rx, USA) was orally administered, allowed to dissolve, swallowed with saliva, followed with 240 mL of drinking water at room temperature. **Treatment (B):** Single dose of Zofran ODT® (Containing Ondansetron 8 mg) Orally Disintegrating Tablets (Manufactured by Cardinal Health Blagrove, Swindon, Wiltshire, UK, SN58RU for Glaxo SmithKline, Research Triangle Park, NC 27709, Made in England) was orally administered, allowed to dissolve, swallowed with saliva, followed with 240 mL of drinking water at room temperature.		
Duration of Treatment: (from date of check in to last participant's study exit) Period-I: 15 Oct 2008 to 17 Oct 2008 Period-II: 22 Oct 2008 to 24 Oct 2008		
Bioanalytical Methods: Plasma samples were analyzed for Ondansetron using a validated analytical method developed at (b) (4) Analysis was done under ultra violet (UV) filtered lighting conditions		

Name of Sponsor: MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	**Name of Finished Product:** Ondansetron ODFS 8mg film.	**Name of Active Ingredient:** Ondansetron
Pharmacokinetic Blood Sampling: A total of 18 blood samples (4 mL each) were collected under golden yellow light (with UV filters) in each period. Blood samples were collected as per the following schedule in each period: The first blood sample was collected within 1 hour prior to drug administration (0.0 hour) and the others at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 15.0, 18.0 and 24.0 hours post dose.		
Pharmacokinetic Analysis: Based on the plasma concentrations of Ondansetron, the following pharmacokinetic parameters were calculated by using "Non-compartmental model" for Treatments A and B: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, k_{el} and $t_{½,}$. All pharmacokinetic analysis was carried out using WinNonlin Ent Version 4.1.		
Safety Assessments: The safety assessments included monitoring of adverse events including adverse drug reactions, periodic physical examination, vital signs monitoring at regular pre-determined intervals and whenever appropriate. Pre study 12-lead ECG, Chest X-ray, Urinalysis and Serology were conducted for screening of volunteers. Pre study Hematology and Serum Chemistry assessments were done to select study participants with baseline values within reference ranges or clinically insignificant values if outside the reference range and post study these were repeated to determine any clinically significant abnormality. Urine Drug Screening and urine pregnancy screen (for female volunteers only) were done at the time of check-in of both the study periods to identify study participants for any substance abuse. A clinical assessment, which includes medical history, general and systemic examination was done at the pre-study screening and post study examination. These investigations were carried out for ensuring safety of study participants and scientific integrity of the study.		
Descriptive Statistics: The descriptive statistics (such as N, mean, SD, minimum, maximum, median, %CV) were calculated for all the PK parameters for each test and reference treatments. Additionally geometric mean was calculated for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. For T_{max} median was reported as descriptive statistics.		
Linear mixed effect model was used to assess the relative bioavailability of Treatment A (Test) versus Treatment B (Reference) for Ondansetron. The PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were natural log transformed before analysis. The model included terms for sequence, period and treatment as fixed effects and study participants nested within sequence as random effect. Within the framework of mixed effects model, least squares means (LSMeans) for Treatment A and B, the difference between LSMeans of test Treatment A versus reference Treatment B and the corresponding 90% CIs for the difference between LSmeans were calculated in natural log scale. The LSMeans, the LSMean differences, and the 90% CIs obtained in the natural log scale were exponentiated to obtain geometric means, the ratio estimates and the 90% CI of ratio estimates in the original scale. If the 90% CIs of the ratio estimates of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were all within 80.00 to 125.00% range for Ondansetron, then Treatment A was concluded as bioequivalent to Treatment B.		

Name of Sponsor:	Name of Finished Product:	Name of Active Ingredient:
MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	Ondansetron ODFS 8mg film.	Ondansetron

Figure I: Mean Plasma Ondansetron Concentrations Vs Time Plot – Linear Scale



Pharmacokinetic Results:

Table 1 Mean (SD)* of Pharmacokinetic Parameters of Ondansetron

PK Parameter (Units)	Ondansetron	
	Treatment A (Test)	Treatment B (Reference)
C_{max} (ng/mL)	26.017 (9.5337)	25.694 (8.6945)
AUC_{0-t} (ng.hr/mL)	201.020 (92.6555)	212.120 (96.4494)
$AUC_{0-\infty}$ (ng.hr/mL)	213.713 (102.2708)	225.891 (110.8730)
T_{max} (Hour)	2.67 (1.00, 4.02)	2.67 (0.67, 6.00)
$t_{1/2}$ (Hour)	5.089 (0.9794)	5.149 (0.9870)
Kel (1/hr)	0.142 (0.0315)	0.139 (0.0270)

*For T_{max} Median (Min, Max) are presented.

NOTE: The above data is excerpted from Table 14.2.2-1 and 14.2.2-2, Section 14.2.

Statistical Results:

Table 2 Statistical Analysis Results for the Assessment of Bioequivalence Based on Pharmacokinetic Parameters of Ondansetron

PK Parameter	Least Squares Geometric Means of Treatment:		Comparison	Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test (A)	Reference (B)				
C_{max} (ng/mL)	24.4389	24.3941	A Vs B	100.18	16.03	(94.68, 106.00)
AUC_{0-t} (ng.hr/mL)	182.5014	195.0514	A Vs B	93.57	14.29	(88.97, 98.40)
$AUC_{0-\infty}$ (ng.hr/mL)	193.1032	205.9382	A Vs B	93.77	14.32	(89.15, 98.63)

NOTE: The above results are excerpted from Table 14.2.3-1, Section 14.2

The 90% CI for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within 80.00-125.00% range.

Name of Sponsor: MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	Name of Finished Product: Ondansetron ODFS 8mg film.	Name of Active Ingredient: Ondansetron

Safety Results:

In this study test formulation of ondansetron was equally as well tolerated as that of the reference, upon single-dose administration to healthy, adult, human study participants.

A total of 09 AEs in 08 study participants were reported during post clinical assessment (i.e. ALT increased for participants 02 & 31, eosinophil count increased for participants 08, 15, 25 & 44, lymphocyte count increased for participants 24 & 47 and WBC count increased in participant 25). Participant 24 was withdrawn from the study before administration of investigational product in period 2 as he tested positive for recent substance abuse. Considering this temporal association with post clinical laboratory changes in lymphocyte count increase was much weaker in participant 24 than in participant 47 who was administered investigational product in period 2 as well. Based upon strength of temporal association, participant 24 and 47 were categorized as unrelated and unlikely respectively. These AEs were graded as mild changes (except participants 08 and 25). The AEs observed for participants 08 & 25 were graded as moderate changes. These changes in laboratory values with respect to eosinophil count were graded as moderate as the magnitude of change in the post clinical value was approximately three times the upper limit of reference range and was considered as unlikely related to study drug by the investigator. Of these, one was judged to be unrelated (participant 24), 2 were judged to be possibly related (participants 02 & 31) and 6 were judged to be unlikely related (participants 08, 15, 25, 44, 47) to the study drug by the investigator. The outcomes of all cases were resolved with no sequelae. (See Appendix 16.2 entitled Subject Data Listings 16.2.7 Individual Subjects Adverse Events and Appendix 14.3 entitled Safety Summaries Table 14.3.1 Number of Distinct Subjects with Adverse Events and Table 14.3.3 Out of Range Laboratory Values).

Name of Sponsor:	Name of Finished Product:	Name of Active Ingredient:
MonoSol Rx, LLC 6560 MELTON ROAD PORTAGE, IN 46368 USA.	Ondansetron ODFS 8mg film.	Ondansetron

Conclusion:

A single dose of Ondansetron Orally Dissolving FilmStrip (ODFS) 8mg (Manufactured by MonoSol Rx, USA) (test formulation) was determined to be bioequivalent and equally tolerated to a single dose of Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] (Manufactured by Cardinal Health Blagrove, Swindon, Wiltshire, UK, SN58RU for Glaxo SmithKline, Research Triangle Park, NC 27709, Made in England) (reference formulation) when both products were tested under fed conditions in healthy, adult, human study participants.

The rate and extent of absorption parameters i.e. $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ under fed condition were equivalent for both reference (Zofran ODT®) and test treatment of ondansetron.

The 90% CI of Ratio estimates of Ondansetron ODFS 8mg film versus Zofran ODT® (Containing Ondansetron 8 mg) Orally Disintegrating Tablets were [94.68, 106.00], [88.97, 98.40] and [89.15, 98.63] for $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty,}$ respectively. All of these were within acceptable range of 80.00 to 125.00 % for $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$. Thus based on these criteria bioequivalence is established in this study.

Overall, a single dose of Ondansetron Orally Dissolving FilmStrip (ODFS) 8mg (Manufactured by MonoSol Rx, USA) and a single dose of Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] (Manufactured by Cardinal Health Blagrove, Swindon, Wiltshire, UK, SN58RU for Glaxo SmithKline, Research Triangle Park, NC 27709, Made in England), when given under fed condition seem to have been equally tolerated by both groups comprising of 45 healthy, adult human participants. Of 48 participants, one "study participant 24" was detected positive for recent substance abuse in urine, one "study participant 36" was absent on period II admission day due to personal reasons and one "study participant 38" was withdrawn from the study in period II due to non compliance in consumption of high fat breakfast, hence these participants were considered as incomplete cases as not available for administration of second treatment.

Date of Final Report: 28 Jan 2009

Study 04795/08-09

Name of Sponsor: MonoSol Rx, LLC 6560 Melton Road Portage, IN 46368 USA.	**Name of Finished Product:** Ondansetron ODFS 8mg film.	**Name of Active Ingredient:** Ondansetron.
Title of Study: An open-label randomized, single oral dose, three way crossover comparative water-effect bioavailability study to compare ondansetron Orally Dissolving Filmstrip (ODFS) 8mg (MonoSol Rx, USA) with and without water with Zofran Orally Dissolving Tablets (ODT®) (Containing Ondansetron 8 mg) (Glaxo SmithKline, USA) without water in 18 adult, healthy human study participants under fasting conditions.		
Investigators: Principal Investigator: – Dr. Salil Budhiraja, MD Medical Investigator: – Dr. B. Kamalesh kumar, MD		
Study Centre: **Clinical Facility:** (b) (4)		**Bio-Analytical, PK & Statistical Facility:** (b) (4)
Publication (Reference): 1: Physicians' Desk Reference. 61st ed. Montvale, NJ: Thomson PDR; 2007. Zofran ODT ® (Ondansetron) Orally Disintegrating Tablets; page no:.1639-1642		
Phase of the Study: Bioavailability study intended for NDA.		
Study Period: Study Start Date: 19 Aug 2008 (Initial date of Volunteer Screening) Study Completion Date: 30 Aug 2008 (Final date of Last Participant Study Exit)		
Objectives: • To compare effect of water on the single dose bioavailability of Ondansetron ODFS 8mg (MonoSol Rx, USA) administered with and without water to Zofran ODT® 8mg without water in healthy male and female adult, human study participants under fasting conditions. • To monitor clinical status, adverse events and laboratory investigations, and to assess the relative safety and tolerance of the study drug formulations under fasting conditions. • To estimate intra-subject coefficients of variation (CV).		

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient:**
MonoSol Rx, LLC 6560 Melton Road Portage, IN 46368 USA.	Ondansetron ODFS 8mg film.	Ondansetron.

Methodology:

All study related procedures, restrictions, duration, dates and timings, information on the study formulation and confidentiality of participant data were explained clearly to the volunteers by clinical personnel at the time of obtaining informed consent. Volunteers who signed the consent form and showed their willingness to participate in the study were enrolled. Volunteers who satisfied the inclusion and exclusion criteria and found to be healthy on physical examination with laboratory investigation values within reference limits were considered eligible to be admitted into the study. Volunteers whose pre-study laboratory values were outside the reference range were allowed to participate, provided these values were determined to be clinically insignificant by the Medical Investigator. The eligible volunteers reported to the study site on 22 Aug 2008, 25 Aug 2008 and 28 Aug 2008 for Period I, Period II & Period III, respectively, between 07:30 am to 04:30 pm.

Participants and Study Activities:

Participants were served dinner between 8:00 pm to 8:30 pm, to ensure a minimum of 10.0 hours of fasting prior to administration of a single dose of either the test or reference product. Participants were dosed as per the randomization schedule with a 3 day wash out period between each administration under fasting conditions. Study restrictions with respect to fluid intake and physical activity were implemented throughout their stay in the Clinical Pharmacology Unit.

Blood samples were obtained as per protocol, centrifuged and plasma was separated. All plasma samples, meant for estimation of Ondansetron levels, were stored at temperature ranging between –18.8°C and –23.7°C (from the date of first sample collection until the last day of analysis).

Number of Participants Planned:

The planned sample size was 18. Total 18 participants were enrolled in the study and 17 of them completed clinical phase of the study successfully.

Number of Samples from Participants Analyzed:

Plasma samples of 18 participants were analyzed. Pharmacokinetic & Statistical analyses included a maximum of 17 participants' data (Participants 1 – 18 except 08).

Main Criteria for Inclusion: Healthy adult participants between 18-45 years of age who were willing to participate in the study by providing written informed consent.

Investigational Products, Dose, Mode of Administration and Batch/Lot Number:

Test Product:	**Reference Product:**
Ondansetron ODFS 8mg Lot No: E08DD201-158 Manufactured By: MonoSol Rx, LLC, USA	Zofran ODT® (Containing Ondansetron 8 mg) Lot No.:511932-8211 Manufactured For: Glaxo SmithKline RTP, NC 27709.

Name of Sponsor:	Name of Finished Product:	Name of Active Ingredient:
MonoSol Rx, LLC 6560 Melton Road Portage, IN 46368 USA.	Ondansetron ODFS 8mg film.	Ondansetron.

The above products were administered after an overnight fasting for at least 10 hours: as following study treatments in each study period.

Test Treatment (A): Single oral dose of Ondansetron ODFS 8mg (MonoSol Rx, USA) administered without water.

Test Treatment (B): Single oral dose of Ondansetron ODFS 8mg (MonoSol Rx, USA) was orally administered, allowed to dissolve, swallowed with saliva, followed with water.

Reference Treatment (C): Single oral dose of Zofran ODT® (Containing Ondansetron 8 mg) (Glaxo SmithKline, USA) administered without water.

Duration of Treatment:
(from date of check in to last participant's study exit)
Period-I: 22 Aug 2008 to 24 Aug 2008
Period-II: 25 Aug 2008 to 27 Aug 2008
Period-III: 28 Aug 2008 to 30 Aug 2008

Bioanalytical Methods: Plasma samples were analyzed for Ondansetron using a validated analytical method developed at (b) (4)

Pharmacokinetic Blood Sampling: A total of 18 blood samples (4 mL each) were collected in each period.
Blood samples were collected as per the following schedule in each period:
The first blood sample was collected within 1 hour prior to drug administration (0.0 hour) and the others at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 15.0, 18.0 and 24.0 hours post dose.

Pharmacokinetic Analysis: Based on the plasma concentrations of Ondansetron, the following pharmacokinetic parameters were calculated by using "Non-compartmental model" for Treatments A, B and C: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, k_{el} and $t_{½}$. All pharmacokinetic analyses were carried out using WinNonlin® Ent Version 4.1.

Name of Sponsor:	Name of Finished Product:	Name of Active Ingredient:
MonoSol Rx, LLC 6560 Melton Road Portage, IN 46368 USA.	Ondansetron ODFS 8mg film.	Ondansetron.

Safety Assessments:

The safety assessments included monitoring of adverse events including adverse drug reactions, periodic physical examination, vital signs monitoring at regular pre-determined intervals and whenever appropriate as determined by medical investigator/study physician monitoring study participants during medical surveillance. Pre study 12-lead ECG, chest x-ray, urinalysis and serology were conducted for screening of volunteers. Pre study hematology and serum chemistry assessments were done to select volunteers whose baseline values were within normal ranges or who had baseline values outside normal ranges that were determined to be clinically insignificant. For those with values outside the reference ranges, assessments were repeated post study to determine if any clinically significant abnormality existed. Urine Drug Screening was done at the time of check-in of all the study periods to identify participants for any substance abuse. Urine pregnancy screen (for female volunteers only) was scheduled at the time of screening, admission for period-1, period 2, period-3 and after the last sample had been collected.

A clinical assessment, which included general and systemic examination were done at the pre-study screening and post study examination. These investigations were carried out for safety of participants and scientific integrity of the study.

Descriptive Statistics:

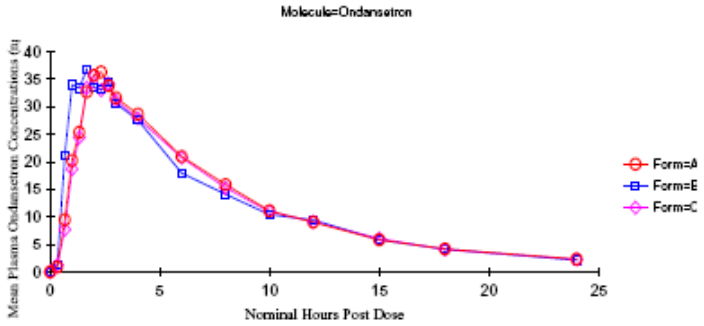
The descriptive statistics (such as N, mean, SD, minimum, maximum, median, %CV) were calculated for all the PK parameters for each test and reference treatments. Additionally, geometric mean was calculated for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. For T_{max} median was reported as descriptive statistics

Statistical Analysis:

A linear mixed effects model that includes fixed effects terms for Sequence, Treatment, Period and a random effects term for Subject (Sequence) was used. Within the framework of this model and consistent with the two one-sided tests for bioequivalence, 90% confidence intervals for the difference between the treatment least-squares means for the comparisons Treatment A vs Treatment B, Treatment A vs Treatment C and Treatment B vs Treatment C were calculated for ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Ondansetron. The differences and the confidence intervals were exponentiated to obtain point estimates of the ratio of the test over reference geometric means and the 90% CI for the ratio, respectively. If the 90% CIs of the ratio estimates of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were all within 80.00 to 125.00% range for Ondansetron, then the Treatments were concluded as bioequivalent to each other.

Name of Sponsor:	Name of Finished Product:	Name of Active Ingredient:
MonoSol Rx, LLC 6560 Melton Road Portage, IN 46368 USA.	Ondansetron ODFS 8mg film.	Ondansetron.

Figure I: Mean Plasma Ondansetron Concentrations Vs Time Plot – Linear Scale



Pharmacokinetic Results:

Table - 1 Mean (SD)[*] of Pharmacokinetic Parameters of Ondansetron

PK Parameter (Units)	Ondansetron		
	Treatment A (Test)	Treatment B (Test)	Treatment C (Reference)
C_{max} (ng/mL)	40.866 (13.3089)	42.843 (15.9103)	39.382 (12.3572)
AUC_{0-t} (ng.hr/mL)	290.687 (106.5203)	291.069 (99.5911)	285.457 (105.3048)
$AUC_{0-\infty}$ (ng.hr/mL)	311.349 (119.7910)	310.394 (112.7499)	306.497 (121.8256)
T_{max} (Hour)	2.00 (1.00, 2.67)	1.67 (0.67, 3.00)	1.67 (1.67, 3.00)
$t_{1/2}$ (Hour)	5.567 (1.0863)	5.738 (0.9205)	5.460 (1.3789)
k_{el} (1/hr)	0.129 (0.0243)	0.124 (0.0208)	0.135 (0.0357)

[*] For T_{max} Median (Min, Max) are presented.

NOTE: The above data is excerpted from Table 14.2.2-1, 14.2.2-2 and 14.2.2-3, Section 14.2.

Statistical Results:

Table - 2 Statistical Results of Assessment of Comparative bioavailability of Ondansetron Under Fasting Conditions (Ondansetron ODFS 8 mg Film administered without water (Test A) with Zofran ODT ® (Containing Ondansetron 8 mg) Orally Disintegrating Tablets administered without water (Reference C))

PK Parameter	Least Squares Geometric Means of Treatment:		Comparison	Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test (A)	Reference (C)				
C_{max} (ng/mL)	39.0534	37.7783	A Vs C	103.38	17.22	(93.57, 114.21)
AUC_{0-t} (ng.hr/mL)	275.7847	269.5142	A Vs C	102.33	10.08	(96.50, 108.51)
$AUC_{0-\infty}$ (ng.hr/mL)	293.7346	286.9189	A Vs C	102.38	10.50	(96.31, 108.82)

NOTE: The above results are excerpted from Table 14.2.3-1, Section 14.2

The 90% CI for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within 80.00-125.00% range.

Name of Sponsor:	Name of Finished Product:	Name of Active Ingredient:
MonoSol Rx, LLC 6560 Melton Road Portage, IN 46368 USA.	Ondansetron ODFS 8mg film.	Ondansetron.

Table - 3 Statistical Results of Assessment of Comparative bioavailability of Ondansetron Under Fasting Conditions (Ondansetron ODFS 8 mg Film administered with water (Test B) with Zofran ODT ® (Containing Ondansetron 8 mg) Orally Disintegrating Tablets administered without water (Reference C))

PK Parameter	Least Squares Geometric Means of Treatment:		Comparison	Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test (B)	Reference (C)				
C_{max} (ng/mL)	40.1524	37.7783	B Vs C	106.28	17.22	(96.20, 117.43)
AUC_{0-t} (ng.hr/mL)	276.0636	269.5142	B Vs C	102.43	10.08	(96.60, 108.62)
$AUC_{0-\infty}$ (ng.hr/mL)	292.4623	286.9189	B Vs C	101.93	10.50	(95.90, 108.35)

NOTE: The above results are excerpted from Table 14.2.3-2, Section 14.2

The 90% CI for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within 80.00-125.00% range.

Table - 4 Statistical Results of Assessment of Comparative bioavailability of Ondansetron Under Fasting Conditions (Ondansetron ODFS 8 mg Film administered without water(Test A) with Ondansetron ODFS 8 mg Film administered with water (Test B))

PK Parameter	Least Squares Geometric Means of Treatment:		Comparison	Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test (A)	Reference (B)				
C_{max} (ng/mL)	39.0534	40.1524	A Vs B	97.26	17.22	(88.03, 107.46)
AUC_{0-t} (ng.hr/mL)	275.7847	276.0636	A Vs B	99.90	10.08	(94.21, 105.93)
$AUC_{0-\infty}$ (ng.hr/mL)	293.7346	292.4623	A Vs B	100.44	10.50	(94.49, 106.76)

NOTE: The above results are excerpted from Table 14.2.3-3, Section 14.2

The 90% CI for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within 80.00-125.00% range.

Name of Sponsor:	Name of Finished Product:	Name of Active Ingredient:
MonoSol Rx, LLC 6560 Melton Road Portage, IN 46368 USA.	Ondansetron ODFS 8mg film.	Ondansetron.

Safety Results:

In this study, Ondansetron ODFS was equally as well tolerated as that of reference, upon single-dose administration to healthy, adult, human participants.

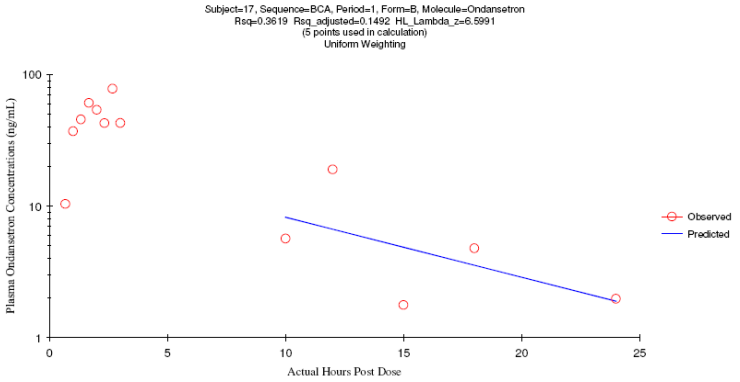
A total of 05 AEs in 04 study participants were reported during post clinical assessment (i.e. ALT levels were beyond the limits of reference range for participants 01, 10 & 13, Increased AST levels for participant 13 and WBC count increased for participant 11). These AEs were graded as mild changes. Of these, 4 AEs were judged to be possibly related (for participants 01, 10 & 13) and one AE was judged to be unlikely related (for participant 11) to the study drug by the investigator. The outcome of event was categorized as unknown for participants 01 & 11 as the participants were lost on follow up, whereas in remaining participant's laboratory changes were resolved with no sequelae (i.e. in participants 10 & 13). (See Appendix 16.2 entitled Subject Data Listings 16.2.7 Individual Subjects Adverse Events and Appendix 14.3 entitled Safety Summaries Table 14.3.1 Number of Distinct Subjects with Adverse Events and Table 14.3.3 Out of Range Laboratory Values).

Conclusion:

In the present bioavailability study 17 participants completed all treatments. Both test and reference formulations of Ondansetron were given as a single dose under fasting conditions. Ondansetron ODFS 8mg (MonoSol Rx, USA) (test formulation) administered without water and with water (i.e., Treatment A & B, respectively) was determined to be bioequivalent to a single dose of Zofran ODT® (Containing Ondansetron 8 mg) (Glaxo SmithKline, USA) administered without water (Treatment C), when the products were tested under fasting conditions in healthy, adult, human participants. In addition, both modes of administration i.e. with and without water of Ondansetron ODFS 8 mg were bioequivalent.

Reviewer's comment: The AUC for subject 17 under treatment B is highly unreliable due to several non-reportable missing plasma concentrations and erratic plasma concentrations in elimination phase. The sponsor included the subject for BE assessment.

However, the inclusion/exclusion of this subject does not change the overall conclusion on the BE assessment.



4.3 OCP Filing Form

Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-524	Brand Name	
OCP Division (I, II, III)	DCP III	Generic Name	Ondansetron
Medical Division	GI	Drug Class	Receptor antagonist (5-HT3)
OCP Reviewer	Lanyan Fang, Ph.D.	Indication(s)	Prevention of Nausea and Vomiting Associated with Highly and Moderately Emetogenic Cancer Chemotherapy and Radiotherapy; Prevention of Postoperative Nausea and/or Vomitting
OCP Team Leader	Sue-Chih Lee, Ph.D.	Dosage Form	Orally Dissolving Film Strip
Date of Submission	April 7, 2009	Proposed Dosing Regimen	1) Highly emetogenic chemotherapy 24 mg at 30 min prior; 2) Moderately emetogenic chemotherapy: 8 mg dose twice a day followed by 8 mg dose twice a day for 1 to 2 days after the completion of the chemotherapy; 3) Radiotherapy: 8 mg 3 times a day; 4) Postoperative: 16 mg before anesthesia.
Estimated Due Date of OCP Review	December 1, 2009	Route of Administration	Oral
Medical Division Due Date	December 6, 2009	Sponsor	PAR
PDUFA Due Date	February 7, 2010	Priority Classification	S

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	1		
Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	5		Crossover BE-type PK study
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	5		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
QT study				
Simulations				
Reference Articles				
Total Number of Studies		6		

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?				
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA	X			

	legible so that a substantive review can begin?				
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. Information Request:

1) Regarding bioequivalence between three 8-mg ondansetron ODFS strips (given successively) and three 8-mg Zofran ODT tablets given simultaneously.

The proposed dosing regimen of the proposed ondansetron ODFS formulation (test) for prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy is 24 mg given successively as three 8-

mg film strip, while the recommended oral dosage for Zofran (reference) is 24 mg given as three 8-mg tablets, given 30 minutes before the start of single-day highly emetogenic chemotherapy. Although bioequivalence was demonstrated between a single dose of ondansetron ODFS 8 mg and a single dose of Zofran ODT 8 mg in terms of Cmax and AUC, bioequivalence has not been established between three 8-mg ondansetron ODFS film strips (24 mg dose) administered successively and three 8-mg Zofran ODT tablets (24 mg) given simultaneously. It is noted that Tmax was delayed for about 10 minutes for Ondansetron ODFS (median Tmax 1.33 vs 1.17 hr) under fasting conditions. If there is a significant delay in Tmax following successive administration of 3 strips, it is unclear how this would affect the onset of the antiemetic activity. The sponsor should address this issue.

2) According to the current label for Zofran ODT product, gender differences were shown in the disposition of ondansetron given as a single tablet dose.

The extent and rate of ondansetron's absorption is greater in women than men, thus higher Cmax and AUC was resulted in women. Slower clearance, a smaller apparent volume of distribution (adjusted for weight), and higher absolute bioavailability resulted in higher plasma ondansetron levels in women than men. In the submitted two pivotal BE studies, limited female subjects were included: 7 females versus 41 males in the fasting BE study and 12 females versus 36 males in the fed BE study. We request that the sponsor reanalyze the data to see if the gender difference was observed with ondansetron ODFS.

Lanyan Fang, Ph.D.	05/14/2009
Reviewing Clinical Pharmacologist	Date
Sue-Chih Lee, Ph.D.	05/14/2009
Team Leader/Supervisor	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22524	ORIG-1	PAR PHARMACEUTICAL	ZUPLENZ (ONDASETRON) ORALLY-DISSOLVING F

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

/s/

INSOOK KIM
02/01/2010

SUE CHIH H LEE
02/01/2010

Biopharmaceutics Review

NDA:	**22-524**
Supplement No:	**000**
Supplement Type:	**Original Submission**
Submission Date:	**April 7, 2009**
Product name:	**Ondansetron**
Dosage Form:	**Orally Dissolving Film Strip (ODFS)**
Dosage Strength:	**4 mg and 8 mg**
Sponsor:	**PAR Pharmaceutical**

Recommendation

ODFS method uses a modified paddle method (b) (4) (Apparatus 5). The film strip samples (b) (4) dissolution vessels containing 900 mL of 0.1N HCl maintained at 37.0ºC ±0.5ºC while stirring at 50 RPM. The samples are withdrawn at a 10 minute intervals. The specification for the finished drug product is set at NLT (b) (4) (Q) in 10 minutes. This specification was adapted from the USP monograph for Ondansetron ODT.

The formulations for each of the dosage strengths are quantitatively identical, with exactly the same proportions of active pharmaceutical ingredient and inactive excipients, as both strengths are (b) (4) the same composition and method of manufacture. The high strength 8mg and low strength 4 mg products are therefore dose proportional.

The dissolution method and specification are acceptable. The dissolution results indicate that the dissolution characteristics of the product are not dependent on the product strength. Therefore, dissolution profiles in one medium are usually sufficient to support waivers of in vivo testing.

Dissolution profiles of the Ondansetron 8 mg and 4 mg ODFS and ODT were found to have comparable dissolution. Therefore, a waiver of bioequivalence studies for the lower strength 4 mg ODFS is justifiable.

Background

Ondansetron, an inhibitor of 5-HT3 receptors, is approved for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy and radiotherapy and with surgical procedures.

Ondansetron hydrochloride is available as an injectable for intravenous or intramuscular administration, and in two oral forms: an oral solution and a tablet. In addition, ondansetron base is available in the form of an orally dissolving tablet (ODT).

Par Pharmaceutical, Inc. is seeking approval for an Orally Dissolving Film Strip (ODFS) formulation in two strengths 4 mg and 8 mg, containing ondansetron (free base) as the active ingredient. Ondansetron ODFS is a thin, flexible, non-friable polymeric film strip containing dispersed ondansetron which is intended to be placed on the tongue for rapid dissolution in the saliva prior to swallowing for delivery into the gastrointestinal tract. Ondansetron ODFS is formulated to dissolve in the oral cavity in under 30 seconds. Depending on the indication, the ondansetron ODFS dose range is from 8 to 24 mg (or one to three 8 mg films taken successively) up to three times a day.

This NDA is submitted under section 505(b) (2) of the Federal Food, Drug and Cosmetic Act. Included in this application is a request for waiver of evidence of in vivo bioequivalence for the 4 mg dosage form. Data from dissolution testing of ondansetron ODFS 4 mg is provided to support approval of the 4-mg dose strength.

The clinical program for ondansetron ODFS consisted of two pilot pharmacokinetic studies and three bioavailability/bioequivalence studies comparing ondansetron ODFS to the reference comparator, commercially available ZOFRAN ODT® (ondansetron) 8 mg, in fasting and fed conditions, and with versus without water co-administration.

Dose Proportionality Assessment

Ondansetron ODFS is available in the following strengths/dimensions:

- Ondansetron (8 mg ondansetron) ODFS contains 8 mg ondansetron base; dimensions 0.875” x 1.25” (22 mm x 32 mm)
- Ondansetron (4 mg ondansetron) ODFS contains 4 mg ondansetron base; dimensions 0.875” x 0.625” (22 mm x 16 mm)

Ondansetron ODFS has different physical dimensions for each of the dosage strengths. The high strength 8 mg ODFS is exactly twice the length and therefore has exactly twice the surface area of the 4 mg ODFS. The high strength ondansetron 8 mg ODFS is also twice as heavy (at 56.8 mg per strip) compared to the ondansetron 4 mg ODFS (at 28.4 mg per strip).

Both strengths of ondansetron ODFS utilize the same formulation – they are cut from bulk film product rolls of the same composition and method of manufacture.

The unit formula and percentage component composition in ondansetron ODFS for each of the dosage strengths are shown in Table 1 below.

Table 1: Quantitative Formula of Ondansetron Orally Dissolving Film Strip

Formulation strength	High Strength Ondansetron ODFS (8mg ondansetron)		Low Strength Ondansetron ODFS (4mg ondansetron)	
Component	WT %	mg/strip	WT %	mg/strip
Ondansetron Base	(b) (4)	8.00	(b) (4)	4.00
Hydroxypropyl methylcellulose (b) (4)	(b) (4)			
Polyethylene Oxide (b) (4)				
Erythritol (b) (4)				
Peppermint Flavor (b) (4)				
Calcium Carbonate (b) (4)				
Sucralose				
Colloidal Silicon Dioxide (b) (4)				
Titanium Dioxide				
Sodium Bicarbonate				
Monoammonium Glycyrrhizinate (b) (4)				
Xanthan Gum (b) (4)				
Butylated Hydroxytoluene (b) (4)				
Total	100.00%	60[1]	100.00%	30

(b) (4)

Reviewer's Note:
The formulations for each of the dosage strengths are quantitatively identical, with exactly the same proportions of active pharmaceutical ingredient and inactive excipients, as both strengths (b) (4) the same composition and method of manufacture. The high strength 8mg and low strength 4 mg products are therefore dose proportional.

In-Vitro Assessment

The monograph for the ondansetron ODT requires the use of the USP basket method (Apparatus 1), but the ODFS method uses a modified paddle method (b) (4) (Apparatus 5). The film strip samples (b) (4)

(b) (4) dissolution vessels containing 900 mL of 0.1N HCl maintained at 37.0ºC ±0.5ºC while stirring at 50 RPM. The samples are withdrawn at a 10 minute intervals. The specification for the finished drug product is set at NLT (b) (4) (Q) in 10 minutes. This specification was adapted from the USP monograph for Ondansetron ODT.

Dissolution results from the QC testing of the ondansetron ODFS 8 mg lot that was used in the pivotal clinical studies are shown in Table 2. The table also shows dissolution data for the ZOFRAN ODT® 8 mg. In addition, 4 mg ODFS and 4 mg ZOFRAN ODT® data are also shown for comparison. The data indicates that essentially complete drug release occurs within 10 minutes for either of the two dosage form types.

Table 2: In vitro Dissolution for ZOFRAN ODT® and Ondansetron ODFS Used in Pivotal Clinical Studies

Study Reference Number	Product/ Lot Number	Dosage Form	Conditions	No. of Dosage Units	Time points (mins)	Mean % Ondansetron dissolved (b) (4)	Study Report Location
01905/08-09 01906/08-09 04795/08-09	Ondansetron ODFS E08DD201-158	8 mg ODFS	Dissolution Apparatus 5 (USP) (b) (4) Speed of Rotation: 50 RPM Medium: 0.1 N HCl Medium Temp.: 37 °C ± 0.5°C	12	5 10 15 30 60 90		ARD-0311-09
01905/08-09 01906/08-09 04795/08-09	Zofran ODT 511932-8211	8 mg ODT	Dissolution Apparatus 5 (USP) (b) (4) Speed of Rotation: 50 RPM Medium: 0.1 N HCl Medium Temp.: 37 °C ± 0.5°C	12	5 10 15 30 60 90		ARD-0311-09
N/A	Ondansetron ODFS E08FL101-150	4 mg ODFS	Dissolution Apparatus 5 (USP) (b) (4) Speed of Rotation: 50 RPM Medium: 0.1 N HCl Medium Temp.: 37 °C ± 0.5°C	12	5 10 15 30 60 90		ARD-0311-09
N/A	Zofran ODT 837870-9037	4 mg ODT	Dissolution Apparatus 5 (USP) (b) (4) Speed of Rotation: 50 RPM Medium: 0.1 N HCl Medium Temp.: 37 °C ± 0.5°C	12	5 10 15 30 60 90		ARD-0311-09

Additional dissolution testing was undertaken on the ondansetron ODFS to compare it versus the Zofran ODT and to examine the rate, extent and variability of drug release. The dissolution measurements of the two products (test and reference, two strengths) were made under the same test conditions mentioned above using twelve (12) units.
Data obtained were used to determine comparability of drug release from the ODFS and ODT formulations. Samples tested for dissolution were:

- Ondansetron 4 mg Orally Dissolving Film Strip (ODFS) – Lot E08FL101-150
- Ondansetron 8 mg Orally Dissolving Film Strip (ODFS) – Lot E08DD201-158 (used in clinical studies 01905/08-09, 01906/08-09 and 04795/08-09).
- Zofran® Ondansetron 4 mg Orally Disintegrating Tablets (ODT) – Lot 837870-9037
- Zofran ® Ondansetron 8 mg Orally Disintegrating Tablets (ODT) – Lot 511932 (used in clinical studies 01905/08-09, 01906/08-09 and 04795/08-09).

The individual data from these dissolution experiments are tabulated along with calculated statistics of minimum value, maximum value, mean and the coefficient of variation in Tables 3, 4, 5, and 6 below.

Table 3: Dissolution Data for Ondansetron ODFS 8 mg

Time Point	Product/ Lot Number	Strength/ Dosage Form	No. of Dosage Units	Mean % dissolved 12 units	Statistic	Statistic Value
5 minutes	Ondansetron E08DD201-158	8 mg ODFS	12	(b) (4)	Mean	(b) (4)
					% RSD	
					Min	
					Max	
10 minutes	Ondansetron E08DD201-158	8 mg ODFS	12		Mean	
					% RSD	
					Min	
					Max	
15 minutes	Ondansetron E08DD201-158	8 mg ODFS	12		Mean	
					% RSD	
					Min	
					Max	
30 minutes	Ondansetron E08DD201-158	8 mg ODFS	12		Mean	
					% RSD	
					Min	
					Max	
60 minutes	Ondansetron E08DD201-158	8 mg ODFS	12		Mean	
					% RSD	
					Min	
					Max	
90 minutes	Ondansetron E08DD201-158	8 mg ODFS	12		Mean	
					% RSD	
					Min	
					Max	

Table 4: Dissolution Data for Zofran ODT 8 mg

Time Point	Product/ Lot Number	Strength/ Dosage Form	No. of Dosage Units	Mean % dissolved 12 units	Statistic	Statistic Value
5 minutes	Zofran 511932-8211	8 mg ODT	12	(b) (4)	Mean	(b) (4)
					% RSD	
					Min	
					Max	
10 minutes	Zofran 511932-8211	8 mg ODT	12		Mean	
					% RSD	
					Min	
					Max	
15 minutes	Zofran 511932-8211	8 mg ODT	12		Mean	
					% RSD	
					Min	
					Max	
30 minutes	Zofran 511932-8211	8 mg ODT	12		Mean	
					% RSD	
					Min	
					Max	
60 minutes	Zofran 511932-8211	8 mg ODT	12		Mean	
					% RSD	
					Min	
					Max	
90 minutes	Zofran 511932-8211	8 mg ODT	12		Mean	
					% RSD	
					Min	
					Max	

Table 5: Dissolution Data for Ondansetron ODFS 4 mg

Time Point	Product/ Lot Number	Strength/ Dosage Form	No. of Dosage Units	Mean % dissolved 12 units	Statistic	Statistic Value
5 minutes	Ondansetron E08FL101-150	4 mg ODFS	12	(b) (4)	Mean	(b) (4)
					% RSD	
					Min	
					Max	
10 minutes	Ondansetron E08FL101-150	4 mg ODFS	12		Mean	
					% RSD	
					Min	
					Max	
15 minutes	Ondansetron E08FL101-150	4 mg ODFS	12		Mean	
					% RSD	
					Min	
					Max	
30 minutes	Ondansetron E08FL101-150	4 mg ODFS	12		Mean	
					% RSD	
					Min	
					Max	
60 minutes	Ondansetron E08FL101-150	4 mg ODFS	12		Mean	
					% RSD	
					Min	
					Max	
90 minutes	Ondansetron E08FL101-150	4 mg ODFS	12		Mean	
					% RSD	
					Min	
					Max	

Table 6: Dissolution Data for Zofran ODT 4 mg

Time Point	Product/ Lot Number	Strength/ Dosage Form	No. of Dosage Units	Mean % dissolved 12 units	Statistic	Statistic Value
5 minutes	Zofran 837870-9037	4 mg ODT	12	(b) (4)	Mean	(b) (4)
					% RSD	
					Min	
					Max	
10 minutes	Zofran 837870-9037	4 mg ODT	12		Mean	
					% RSD	
					Min	
					Max	
15 minutes	Zofran 837870-9037	4 mg ODT	12		Mean	
					% RSD	
					Min	
					Max	
30 minutes	Zofran 837870-9037	4 mg ODT	12		Mean	
					% RSD	
					Min	
					Max	
60 minutes	Zofran 837870-9037	4 mg ODT	12		Mean	
					% RSD	
					Min	
					Max	
90 minutes	Zofran 837870-9037	4 mg ODT	12		Mean	
					% RSD	
					Min	
					Max	

A profile comparison using the f_2 factor was not calculated since this dosage form is rapidly dissolving with greater than (b) (4) released in 15 minutes or less. Therefore, a profile comparison is not meaningful and a single point comparison is satisfactory.

Both the ondansetron ODFS 8 mg and the Zofran® ODT 8 mg released greater than (b) (4) ondansetron within 10 minutes. The coefficient of variation at the earliest sampling point (5 minutes) for the ODFS is not more than (b) (4) and at the other time points is not more than (b) (4).

Figure 1 below shows a plot comparing the drug release profiles of the 8 mg ODT versus the ODFS.

Figure 1: Dissolution profile for ondansetron 8 mg ODFS vs. ODT

The 4 mg ODFS and 4 mg ODT also exhibited rapid release of the ondansetron with greater than (b) (4) ondansetron released within 10 minutes thereby readily meeting the finished product specifications. The coefficient of variation for the earliest sampling point (5 minutes) for the ODFS is not more than (b) (4) and at other time points is not more than (b) (4). A plot of the dissolution profile is shown in Figure 2 below.

Figure 2: Dissolution profile for ondansetron 4 mg ODFS vs. ODT

Reviewer's Note:
The 4 mg ODFS performs similarly to the 8 mg ODFS since they are created from the same bulk film formulation simply by cutting to half the size.

Dissolution profiles of the Ondansetron 8 mg and 4 mg ODFS and ODT were found to have comparable dissolution. Both strengths of dosage forms showed (b) (4) within 15 minutes at the given conditions.

Analytical Method

This method is based on the dissolution of Ondansetron 4 mg and 8 mg Film strips in 0.1 N HCl media followed by quantitation by HPLC. Quantitation is performed by external standards using a [redacted] (b) (4) HPLC column with detection wavelength at 300 nm.

The specification is NLT [redacted] (b) (4) dissolved in 10 minutes. The analytical parameters of ondansetron are shown in Table 7 below.

Table 7: The Analytical Parameters for Ondansetron

Lower Limit of Quantification (LLOQ)	0.51 ng/mL
Accuracy	105.10%
Precision	6.27%
Recovery	76.5%
Intra-batch Accuracy	88.71-97.18%
Inter-batch Accuracy	89.21-93.46%
Intra-batch Precision	1.29-4.15%
Inter-batch Precision	1.81-4.46%
Stability	Freeze-thaw stability (3 cycles ≥ 95%) Injector stability (≥ 89.52% at 26 hr) Wet extract stability (≥ 89.93% at 21 hr) Dry extract stability (≥ 89.33% at 21 hr) Bench top stability (≥ 93.11% for 16 hr)

Comment to the Chemistry Reviewer

The biowaiver request for the 4 mg ODFS is acceptable.

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Patrick Marroum, Ph.D.

Biopharmaceutics Expert
Office of New Drug Quality Assessment

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22524	ORIG-1	PAR PHARMACEUTICAL RESOURCES INC	ZUPLENZ (ONDASETRON) ORALLY-DISSOLVING F

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/s/

HOUDA MAHAYNI
09/10/2009

PATRICK J MARROUM
09/10/2009