CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205208Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA:	205208
Generic Name:	Desvenlafaxine Fumarate
Trade Name:	Not Applicable
Strength and Dosage Form:	50 mg and 100 mg Extended Release Tablets
Indication:	Major Depressive Disorder (MDD)
Sponsor:	Teva Pharmaceuticals USA
Submission Type:	Original NDA [505(b)(2)]
Priority Classification:	Standard
Submission Date:	12/12/12
OCP Division:	DCP1
OND Division:	DPP
Reviewer:	Kofi Kumi, Ph.D.
Team Leader:	Hao Zhu, Ph.D.

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Executive Summary

The sponsor submitted Desvenlafaxine fumarate Extended Release (ER) tablets as a 505(b)(2) application using the approved Desvenlafaxine succinate ER (Pristiq ER®) as the reference product. The development program mainly depended on demonstrating bioequivalence between Desvenlafaxine ER and Pristiq ER tablets. Clinical safety and efficacy studies were not conducted for this application. The effect of food on Desvenlafaxine fumarate ER tablet was evaluated. The sponsor is seeking the indication of major depressive disorder which is approved for Pristiq. Our findings are summarized as follows:

- Desvenlafaxine ER tablet is bioequivalent to Pristiq ER at the strengths of 50 mg and 100 mg.
- Desvenlafaxine fumarate ER can be administered with or without food.
- Desvenlafaxine fumarate ER exhibits extended release characteristics similar to the approved Pristiq ER.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) supports a recommendation for approval of Desvenlafaxine fumarate ER at the same dosing recommendation approved for Pristiq ER for the treatment of major depressive disorder (MDD).

1.2 Post Market Studies

No post-marketing studies are recommended by OCP.

1.3 Labeling Recommendations

The following language should be incorporated into the label under Pharmacokinetics, Section 12.3

Desvenlafaxine fumarate extended release 50 mg and 100 mg demonstrated similar exposures (Cmax, AUC) to a 50 mg and 100 mg extended release desvenlafaxine succinate product, respectively.

The mean terminal half of desvenlafaxine after administration of desvenlafaxine fumarate extended release tablet is about 9.8 hours. The median (range) time to peak concentration is 7.5 (4.5 – 14.0) hours after administration of 50 mg desvenlafaxine fumarate extended release tablets

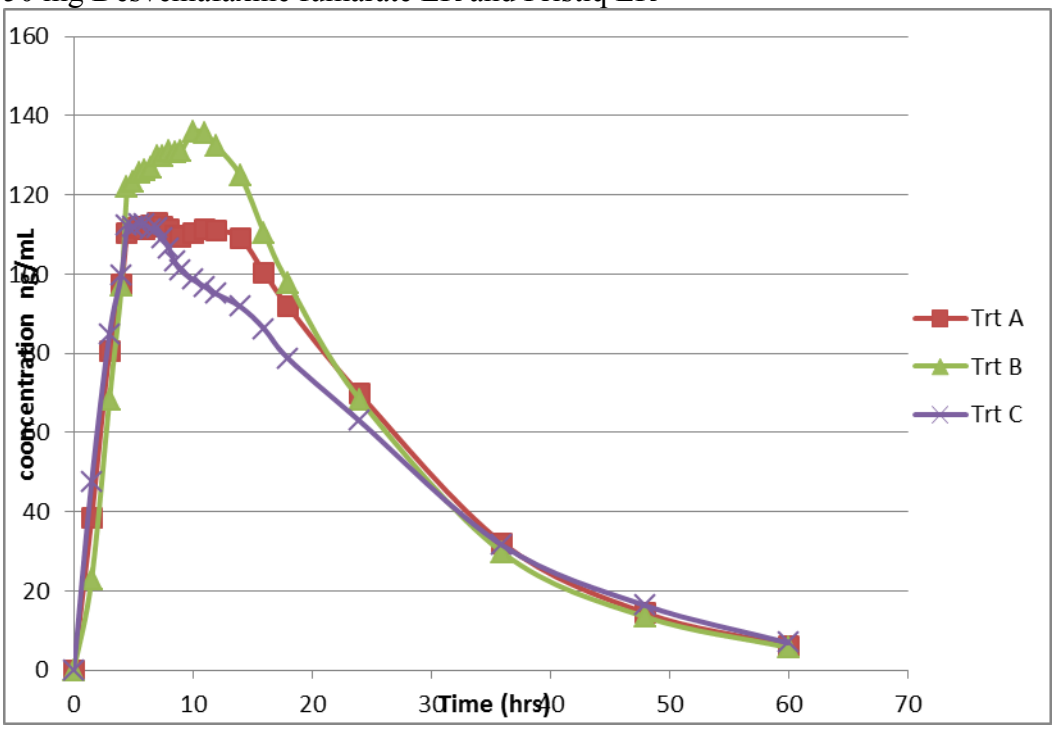
A food-effect study involving administration of Desvenlafaxine fumarate extended-release tablets to healthy subjects under fasting and fed conditions (high-fat meal 800 to 1000 calories) indicated that desvenlafaxine C_{max} was increased by about 19% in the fed state, while the AUCs were similar. This difference in Cmax is not expected to be clinically significant; therefore, Desvenlafaxine fumarate extended-release tablets can be taken with or without food.

1.4 Summary of Clinical Pharmacology and Biopharmaceutics

Bioequivalence and food effect
Desvenlafaxine fumarate Extended Release (ER) tablet was demonstrated to be bioequivalent to Pristiq® (Desvenlafaxine succinate) ER Tablet under fasting at 50 mg and 100 mg strengths, respectively. Tables 1 to 3 contain the statistical results for the comparison of Desvenlafaxine fumarate ER (T) to Pristiq (R) 50 mg and 100 mg ER tablets under fasting conditions and the effect of food on Desvenlafaxine fumarate ER. The 90% confidence interval (CI) of the mean ratio falls within the regulatory criteria of 80% to 125%. Therefore, Desvenlafaxine fumarate ER tablet is bioequivalent to Pristiq ER, the reference drug.

When Desvenlafaxine fumarate ER tablet was administered under fed conditions compared to when given under fasting conditions, Cmax increased by about 19% and AUC by about 7%. The increase in Cmax was significant but it is not expected to be clinically relevant. When the reference drug, Pristiq, was administered under fed compared to fasting conditions, Cmax is reported to increase by about 16% with no significant increase in AUC. Desvenlafaxine fumarate ER 100 mg was also demonstrated to be bioequivalent to Pristiq ER 100 mg under fed conditions (Table 6, QBR section). Therefore, like Pristiq, Desvenlafaxine fumarate ER can be taken with or without food. Figure 1 contains plasma concentration time profile for Desvenlafaxine fumarate ER 50 mg under fed and fasting conditions and Pristiq under fasting conditions.

Figure 1: Mean plasma desvenlafaxine concentration time profile after administration of 50 mg Desvenlafaxine fumarate ER and Pristiq ER



Trt A: Desvenlafaxine fumarate ER 50 mg under fasting conditions
Trt B: Desvenlafaxine fumarate ER 50 mg with food
Trt C: Pristiq ER 50 mg under fasting conditions

The median Tmax of desvenlafaxine after administration of Desvenlafaxine fumarate ER was 1.5 hours longer than that after administration of Pristiq ER 50 mg. The difference is not expected to be clinically relevant. Desvenlafaxine median Tmax was similar after administration of Desvenlafaxine fumarate ER under fed and fasting conditions. After administration of Desvenlafaxine fumarate ER, there was not a significant difference in half-life for desvenlafaxine after administration of Desvenlafaxine fumarate ER or Pristiq ER. This suggests the extended release characteristics for Desvenlafaxine fumarate ER is similar to that of Pristiq ER.

Table 1: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Desvenlafaxine ER or Pristiq ER 50 mg to Healthy Subjects under Fasting conditions.

Parameter	Geometric Mean		Ratio of Geometric Mean (%)	90% Confidence Interval (%)
	Treatment A (n=28)	Treatment C (n=27)	A/C	
Cmax (ng/mL)	126.15	114.73	109.96	102.70 – 117.73
AUCt (ng*hr/mL)	3002.61	2789.71	107.63	101.01 – 114.69
AUC∞ (ng*hr/mL)	3080.93	2886.64	106.73	100.05 – 113.86
Tmax [hr][*]	7.50 (4.5 – 14.0)	6.00 (4.0 – 16.0)		
T ½ [hr][#]	9.84(14)	10.54 (27)		

[*]Median (range), [#]Arithmetic mean (CV%)
Trt A: Desvenlafaxine fumarate ER 50 mg under fasting conditions
Trt C: Pristiq ER 50 mg under fasting conditions

Table 2: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose administration of Desvenlafaxine fumarate ER 50 mg tablet with or without food.

Parameter	Geometric Mean		Ratio of Geometric Mean (%)	90% Confidence Interval (%)
	Treatment A (n=28)	Treatment B (n=28)	B/A	
Cmax (ng/mL)	126.15	150.16	119.03	111.27 – 127.33
AUCt (ng*hr/mL)	3002.61	3230.47	107.59	101.05 – 114.55
AUC∞ (ng*hr/mL)	3080.93	3308.07	107.37	100.73 – 114.45
Tmax [hr][*]	7.50 (4.5 – 14.0)	7.75 (4.5 – 14.0)		
T ½ [hr][#]	9.84 (14)	9.71 (16)		

[*]Median (range), [#]Arithmetic mean (CV%)
Trt A: Desvenlafaxine fumarate ER 50 mg under fasting conditions
Trt B: Desvenlafaxine fumarate ER tablet 50 mg administered with food

Table 3: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Desvenlafaxine ER or Pristiq ER 100 mg to Healthy Subjects under Fasting Conditions (n= 25).

Parameter	Least Squares Geometric Mean		Ratio of Geometric Mean (%)	90% Confidence Interval (%)
	Treatment A (n=25)	Treatment B (n=25)	A/B	
Cmax (ng/mL)	242.72	240.07	101.10	92.14 – 110.94
AUCt (ng*hr/mL)	6568.43	6618.37	99.25	90.39 – 108.97
AUC∞ (ng*hr/mL)	6801.73	6887.11	98.76	89.88 – 108.51
Tmax [hr]*	8.0 (4.5 – 16.0)	6.5 (4.5 – 16.0)		
T ½ [hr]#	10.47 (18.09)	11.15 (21.51)		

*Median (range); #Arithmetic mean (CV%)
Trt A: Desvenlafaxine fumarate ER 100 mg under fasting conditions
Trt B: Pristiq ER 100 mg under fasting conditions

Alcohol Dose Dumping
Dose dumping due to alcohol was not observed based on an *in vitro* study. Refer to Biophmarmaceutics review.

Clinical and Bioanalytical Site Inspections:
The bioequivalence studies were inspected by the Office of Scientific Investigations (OSI). OSI inspection report is attached. OSI recommended that DPP exclude the data for subjects 15 and 34 in Study 53711 due to problems with the analytical runs for these subjects. Table 3 (under Executive Summary section) is the results of the redo of the statistical analysis excluding subjects 15 and 34. Table 4 (under QBR section) contains the statistical analysis that included all the subjects in the study. The results based on the recalculated data are consistent with the results obtained when all the subjects were included in the analysis. Therefore the overall conclusions remain unchanged and Desvenlafaxine fumarate 100 mg ER is bioequivalent to Pristiq ER 100 mg under fasting conditions.

Question Based Review (QBR)

2.1 General Attributes

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

The sponsor submitted a 505(b)(2) application for Desvenlafaxine fumarate Extended Release (ER) tablets. The reference drug for this application is Pristiq® (desvenlafaxine succinate ER)

tablet which is currently approved for the treatment of major depressive disorder (MDD). The application was primarily based on demonstration of bioequivalence between Desvenlafaxine fumarate ER (Teva) and Pristiq and determining the food effect on the product. Clinical safety and efficacy studies were not conducted.

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?

Desvenlafaxine Fumarate is a white to off-white crystalline powder that is slightly soluble (1mg/mL) in water and ethanol. Figure 2 is the structure of desvenlafaxine fumarate.

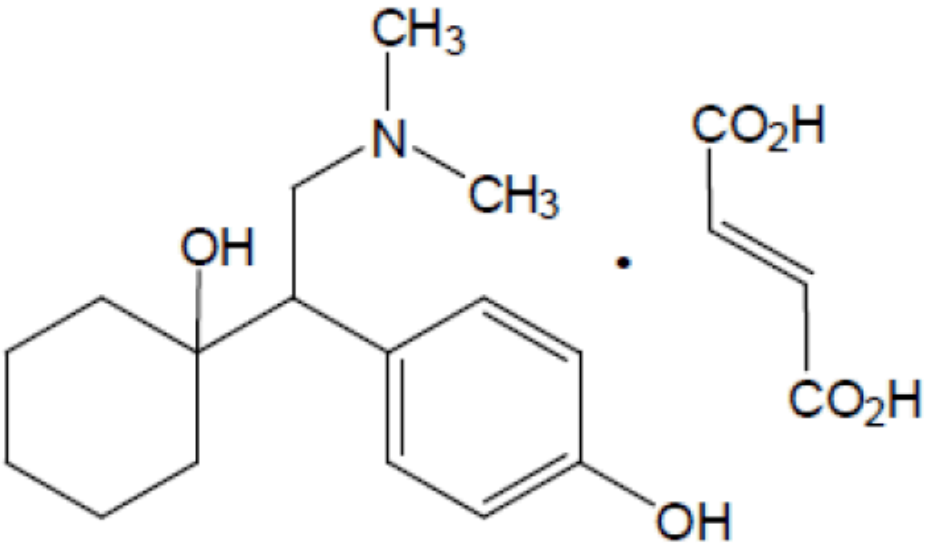


Figure 2: Molecular Structure of Desvenlafaxine Fuamarate

The sponsor has developed an ER tablet formulation that contains desvenlafaxine fumarate as the active moiety. The reference product, Pristiq, contains desvenlafaxine succinate as the active moiety.

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

Desvenlafaxine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). It is indicated for the treatment of major depressive disorder (MDD).

2.1.4 What are the proposed dosage and route of administration?

The recommended dose for desvenlafaxine is 50 mg daily, with or without food administered orally. In clinical studies doses of 50 to 400 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg/day and adverse events and discontinuations were more frequent at higher doses.

2.1.5 What is the reported adverse event profile from the bioequivalence studies?

The sponsor reported that no serious adverse events (AE) were observed in the studies. The sponsor reported that in study 2012-2883 (50 mg BE study), one subject (subject 15) was dismissed from the study after Period 1 dosing due to vomiting. The AE was judged to be mild and it resolved with no action taken. In study 53711 (100 mg fasting BE), the sponsor reported that twenty-four (24) subjects reported 62 adverse events of mild to moderate intensity including; 11 headache, 21 nausea, 8 emesis, 4 diarrhea, 2 AE each of dry mouth, restlessness, lightheaded, and 1 adverse event each of difficulty concentration, loss of appetite, somnolence, restless in legs, syncope, fever, stomach pain, shakiness, disorientation, anorexia, dizziness and, soreness in left hand. The sponsor reported that the adverse events resolved without sequelae. In study 53811 (100 mg fed BE), the sponsor reported that 12 subjects reported 33 adverse events of mild intensity including; 7 adverse events of headache, 11 adverse events of nausea, 3 adverse events of anxiety, 2 adverse events each of visual disturbance and 1 adverse event each of emesis, diarrhea, dizziness, stomach cramps, bilateral jaw paresthesia, diaphoresis, trembling in legs (bilateral), weakness in legs (bilateral), blurred vision and swelling in right eye. These AEs were reported to be mild in intensity. The sponsor reported that the adverse events resolved without sequelae. The sponsor reported that in general Desvenlafaxine fumarate ER was well tolerated. Refer to medical review for Agency's evaluation of safety.

2.2. General Clinical Pharmacology and Biopharmaceutics

2.2.1 What are the design features of the clinical pharmacology and/or bopharmaceutics studies used to support dosing or claims?

The sponsor is seeking approval for treatment of major depressive disorder (MDD) which is currently approved for Pristiq. Therefore, the following bioequivalence studies comparing Desvenlafaxine ER (desvenlafaxine fumarate) to Pristiq (desvenlafaxine succinate) are the studies used to support dosing and claims.

A Pivotal, Open-Label, Single-Center, Randomized, Single-Dose, Two-Period, Two-Treatment, Two-Sequence Crossover Study to Compare the Bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets, Equivalent to 100 mg Desvenlafaxine to Pristiq® Extended-Release Tablets, 100 mg Under Fasted Conditions

A Pivotal, Open-Label, Single-Center, Randomized, Single-Dose, Two-Period, Two-Treatment, Two-Sequence Crossover Study to Compare the Bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets, Equivalent to 100 mg Desvenlafaxine to Pristiq® Extended-Release Tablets, 100 mg Under Fed Conditions

A Single-Dose, Comparative Bioavailability Study of One Formulation of Desvenlafaxine Fumarate Extended Release Tablets, Equivalent to 50 mg Desvenlafaxine and One Formulation of Pristiq® Extended Release Tablets, 50 mg under Fasting and Fed Conditions.

2.2.2 Is Desvenlafaxine Fumarate 100 mg ER bioequivalent to the reference listed drug, Pristiq (desvenlafaxine succinate) 100 mg ER under fasting and fed conditions?

Desvenlafaxine Fumarate ER Tablets, 100 mg were bioequivalent to Pristiq® ER Tablet, 100 mg after administration of single doses of 100 mg desvenlafaxine fumarate ER tablets under fasting and fed conditions.

The sponsor conducted a single dose, randomized, open-label, 2-period, 2-treament, two sequence, crossover bioequivalence study in healthy subjects to demonstrate that Desvenlafaxine fumarate (Teva) was bioequivalent to Desvenlafaxine succinate (Pristiq, Wyeth) under fasting conditions. The mean plasma concentration-time profiles after administration of 100 mg Desvenlafaxine fumarate or 100 mg Pristiq under fasting conditions are provided in Figure 3.

Figure 3: Mean Plasma Concentration versus Time Profiles

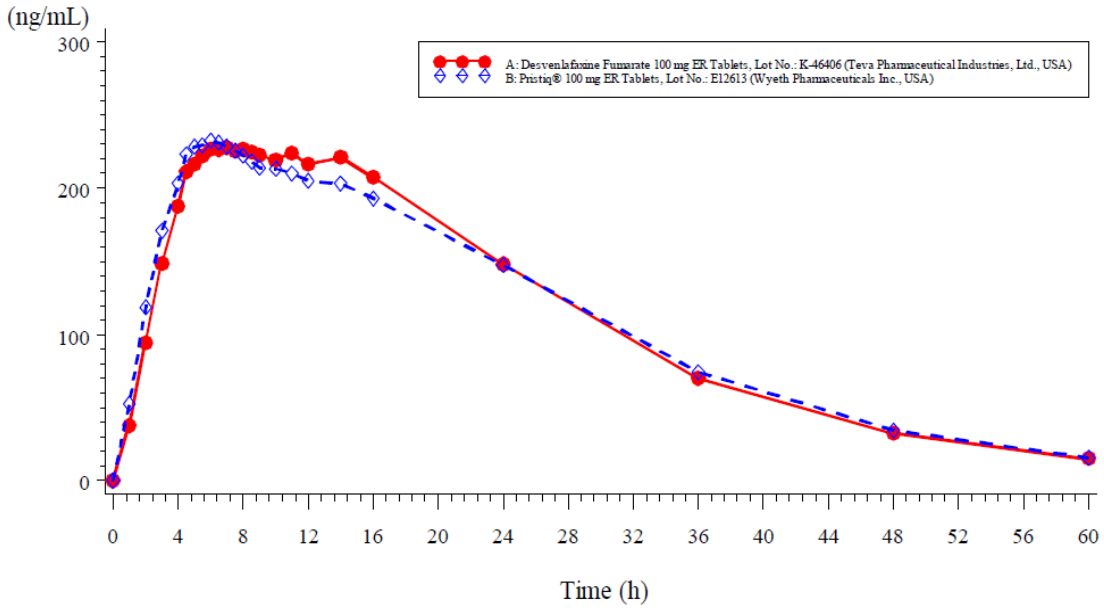


Table 4 contains the statistical analysis for Desvenlafaxine after administration of Desvenlafaxine fumarate ER and Pristiq ER under fasting conditions. This analysis was based on all subjects that completed the study.

Table 4: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Treatments A or B to Healthy Subjects under Fasting Conditions (N=27)

Parameter	Least Squares Geometric Mean		Ratio of Geometric Mean (%)	90% Confidence Interval (%)
	Treatment A	Treatment B	A/B	A/B
C_{max} (ng/mL)	237.68	237.97	99.88	91.56 - 108.95
AUC_{0-t} (h•ng/mL)	6244.12	6430.71	97.10	88.58 - 106.44
AUC_{0-inf} (h•ng/mL)	6451.54	6675.01	96.65	88.12 - 106.01
Treatment A: Desvenlafaxine Fumarate ER Tablets, 100 mg, Test Formulation A Treatment B: Pristiq® ER Tablets, 100 mg, Reference				

The 90% confidence intervals (CIs) of the ratios of Cmax, AUC (0-t), and AUC(0-∞) between test and reference are within the regulatory criteria (80% to 125%) for bioequivalence; therefore, Desvenlafaxine fumarate ER is bioequivalent to Pristiq ER under fasting conditions. The median (range) Tmax for desvenlafaxine after administration of Desvenlafaxine fumarate ER and Pristiq ER were 8.0 (4.5 – 16.0) and 6.5 (4.5 – 16.0) hours, respectively. The mean half-life for desvenlafaxine after administration of Desvenlafaxine fumarate ER and Pristiq ER were 10.3 and 11.0 hours, respectively.

The Office of Scientific Investigation (OSI) inspection revealed that there were problems with the analytical runs for subjects 15 and 34 in Study 53711 (Bioequivalence study evaluating Desvenlafaxine fumarate ER 100 versus Pristiq ER 100 mg under fasting conditions). Therefore, OSI recommended that the data for these subjects be excluded from the data set and the statistical analysis re-done. The results of the recalculated data are provided in Table 3. The results of the recalculated are consistent with the conclusions that Desvenlafaxine fumarate ER (Teva) is bioequivalent to Pristiq ER 100 mg under fasting conditions. The following is the mean plasma concentration time profile excluding subjects 15 and 34.

Figure 4: Mean Plasma Desvenlafaxine Concentration-Time Profiles (Excludes Subjects 15 and 34; n=25)

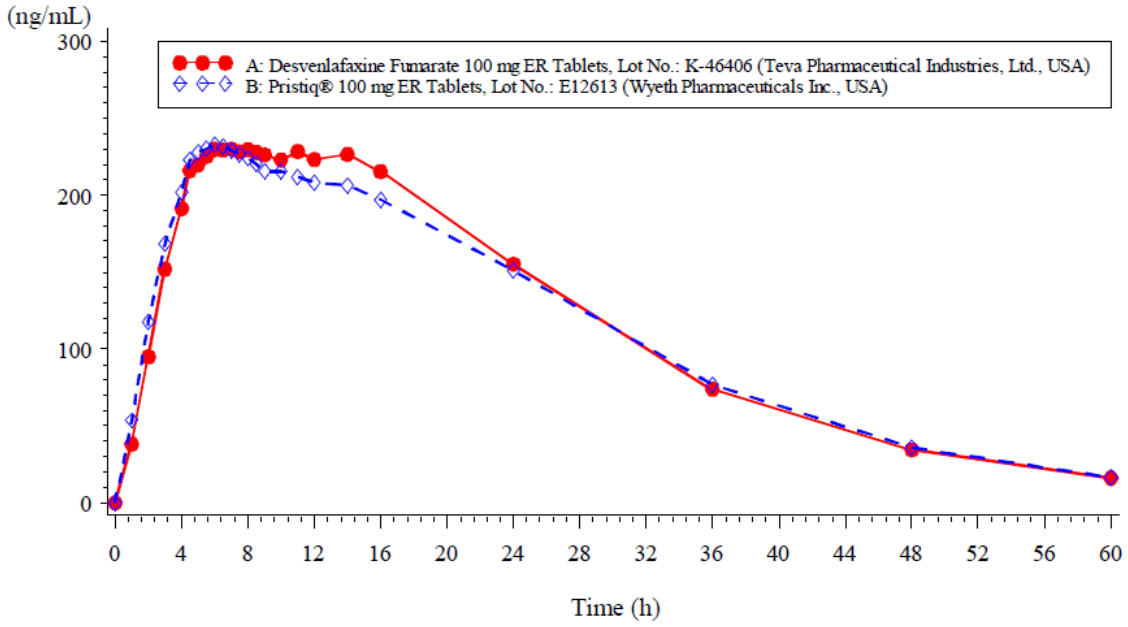


Table 5: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Desvenlafaxine ER or Pristiq ER100 mg to Healthy Subjects under Fasting Conditions (Subjects 15, 34 excluded; n= 25).

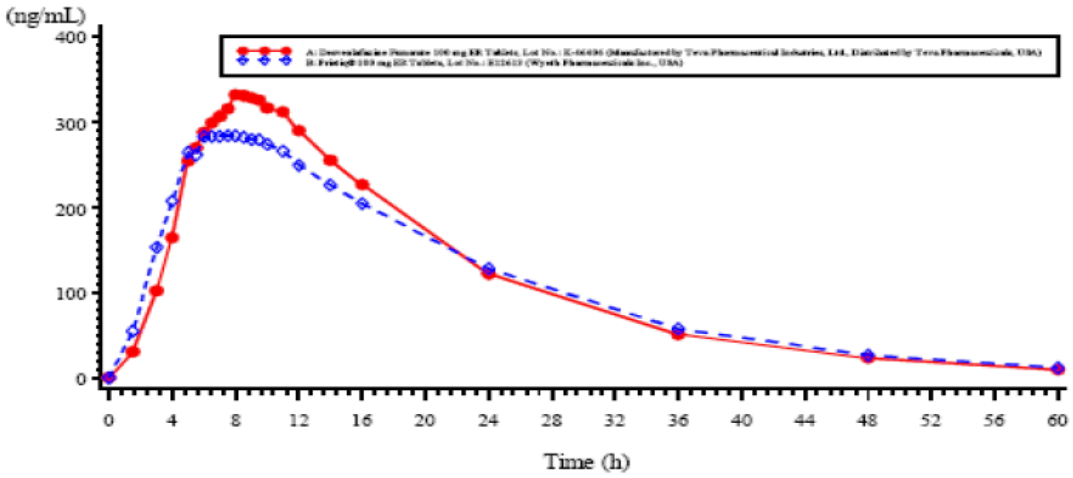
Parameter	Least Squares Geometric Mean		Ratio of Geometric Mean (%)	90% Confidence Interval (%)
	Treatment A (n=25)	Treatment B (n=25)	A/B	
Cmax (ng/mL)	242.72	240.07	101.10	92.14 – 110.94
AUCt (ng*hr/mL)	6568.43	6618.37	99.25	90.39 – 108.97
AUC∞ (ng*hr/mL)	6801.73	6887.11	98.76	89.88 – 108.51
Tmax [hr][*]	8.0 (4.5 – 16.0)	6.5 (4.5 – 16.0)		
T ½ [hr][#]	10.47 (18.09)	11.15 (21.51)		

[*]Median (range); [#]Arithmetic mean (CV%)
Trt A: Desvenlafaxine fumarate ER 100 mg under fasting conditions
Trt B: Pristiq ER 100 mg under fasting conditions

The sponsor also conducted an open-label, single-center, randomized, single dose, two-period, two treatment, two sequence crossover study to assess the bioequivalence of Desvenlafaxine ER 100 mg Tablets (Teva) to Pristiq ER 100 mg tablets under fed conditions. The meal consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk. This is the standard FDA recommended breakfast which contains 800 to 1000 calories. The mean plasma concentration-time profiles after

administration of 100 mg Desvenlafaxine fumarate or 100 mg Pristiq under fed conditions are provided in Figure 5.

Figure 5: Mean Plasma Concentration versus Time Profiles after Administration of Desvenlafaxine Fumarate ER and Pristiq ER under Fed Conditions



Red: Desvenlafaxine fumarate ER; Blue: Pristiq ER

Table 6 contains the statistical analysis for Desvenlafaxine under fed conditions.

Table 6: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Treatments A or B to Healthy Subjects under Fed conditions (N=22).

Parameter	Least Squares Geometric Mean		Ratio of Geometric Mean(%)	90% Confidence Interval(%)
	Treatment A	Treatment B	A/B	A/B
C_{max} (ng/mL)	361.03	320.18	112.76	105.04- 121.05
AUC_{0-t} (h•ng/mL)	6613.93	6509.42	101.61	98.96- 104.32
AUC_{0-inf} (h•ng/mL)	6766.91	6700.88	100.99	98.27- 103.78

Treatment A: Desvenlafaxine Fumarate ER Tablets, 100 mg, Test Formulation A
Treatment B: Pristiq® ER Tablets, 100 mg, Reference

The 90% confidence intervals (CIs) of the ratios of Cmax, AUC (0-t), and AUC(0-∞) between test and reference are within the regulatory criteria (80% to 125%) for bioequivalence; therefore, Desvenlafaxine fumarate ER is bioequivalent to Pristiq ER under fed conditions. The median (range) Tmax for desvenlafaxine after administration of Desvenlafaxine fumarate ER and Pristiq ER under fasting conditions were 8.0 (5 – 16.0) and 7 (5 – 11.0) hours, respectively. The mean half-life for desvenlafaxine after administration under fed conditions of Desvenlafaxine fumarate ER and Pristiq ER were 9.43 and 10.29 hours, respectively.

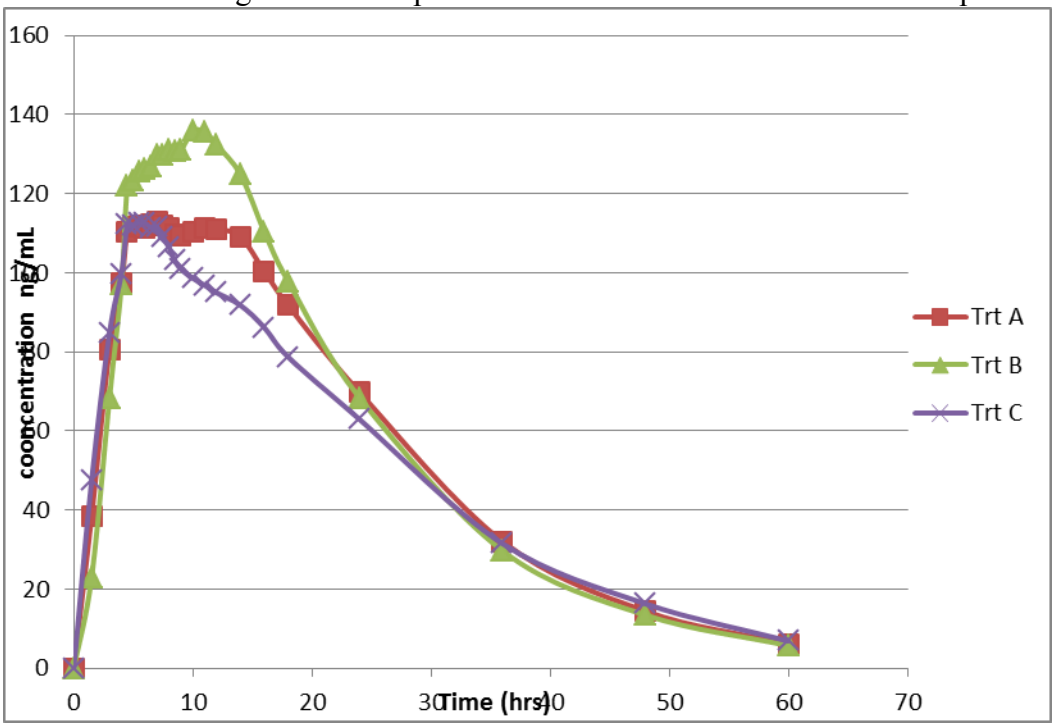
2.2.3 Is Desvenlafaxine fumarate(Teva) 50 mg ER tablet bioequivalent to the reference listed drug, Pristiq® (desvenlafaxine succinate) 50 mg ER under fasting conditions?

Desvenlafaxine fumarate ER Tablets, 50 mg were bioequivalent to Pristiq® ER Tablet, 50 mg after single dose administration under fasting conditions.

The sponsor assessed the bioequivalence of Desvenlafaxine after administration of Desvenlafaxine fumarate ER and Pristiq ER 50 mg under fasting conditions. The study was an open-label, single-dose, randomized, three-period, six-sequence, three-treatment, crossover trial.

The mean plasma concentration-time profiles after administration of 50 mg Desvenlafaxine fumarate or 50 mg Pristiq under fasting conditions and with food are provided in Figure 6.

Figure 6: Mean plasma desvenlafaxine concentration time profile



Trt A: Desvenlafaxine fumarate ER under fasting conditions
Trt B: Desvenlafaxine fumarate ER with food
Trt C: Pristiq ER under fasting conditions

Table 7: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Treatments A or C to Healthy Subjects under Fasting conditions.

Parameter	Geometric Mean		Ratio of Geometric Mean (%)	90% Confidence Interval (%)
	Treatment A (n=28)	Treatment C (n=27)	A/C	
Cmax (ng/mL)	126.15	114.73	109.96	102.70 – 117.73
AUCt (ng*hr/mL)	3002.61	2789.71	107.63	101.01 – 114.69
AUC∞ (ng*hr/mL)	3080.93	2886.64	106.73	100.05 – 113.86
Tmax [hr]*	7.50 (4.5 – 14.0)	6.00 (4.0 – 16.0)		

*Median (range)
Trt A: Desvenlafaxine fumarate ER under fasting conditions
Trt C: Pristiq ER under fasting conditions

The 90% confidence intervals (CIs) of the ratios of Cmax, AUC (0-t), and AUC(0-∞) between test (Trt A) and reference (Trt C) are within the regulatory criteria (80% to 125%) for bioequivalence; therefore, Desvenlafaxine fumarate ER is bioequivalent to Pristiq ER under fasting conditions. The median (range) Tmax for desvenlafaxine after administration of Desvenlafaxine fumarate ER and Pristiq ER were 7.50 (4.5 – 14.0) and 6 (4.0 – 16.0) hours, respectively. The mean half-life for desvenlafaxine after administration under fasting conditions of Desvenlafaxine fumarate ER and Pristiq ER were 9.84 and 10.54 hours, respectively.

2.2.4 Is the exposure to Desvenlafaxine fumarate significantly different after administration of Desvenlafaxine fumarate 50 mg with or without food?

The extent of exposure (AUC) was not significantly different when Desvenlafaxine fumarate ER is administered with or without food. However, the peak concentration (Cmax) was significantly higher (19% higher) when Desvenlafaxine fumarate extended release tablet is administered with food than when administered on an empty stomach. Food did not significantly affect the time to peak concentration (Tmax). The increase in Cmax is not expected to be clinically significant.

Table 8 contains the statistical comparison of the pharmacokinetics of desvenlafaxine after administration of Desvenlafaxine fumarate ER 50 mg tablets with or without food.

Table 8: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose administration of Desvenlafaxine fumarate ER 50 mg tablets with or without food.

Parameter	Geometric Mean		Ratio of Geometric Mean (%)	90% Confidence Interval (%)
	Treatment A (n=28)	Treatment B (n=27)	B/A	
Cmax (ng/mL)	126.15	150.16	119.03	111.27 – 127.33
AUCt (ng*hr/mL)	3002.61	3230.47	107.59	101.05 – 114.55
AUC∞ (ng*hr/mL)	3080.93	3308.07	107.37	100.73 – 114.45
Tmax [hr]*	7.50 (4.5 – 14.0)	7.75 (4.5 – 14.0)		

*Median (range)
Trt A: Desvenlafaxine fumarate ER under fasting conditions
Trt B: Desvenlafaxine fumarate ER tablet administered with food

The 90% confidence intervals (CIs) of the ratios of AUC (0-t), and AUC(0-∞) between test (Trt B) and reference (Trt A) are within 80% to 125% regulatory criteria of no significant difference. However, the 90% confidence interval of the ratio of Cmax between treatment B and treatment A was outside the confidence limits. Therefore, a significant difference was observed when Desvenlafaxine fumarate ER was administered with food compared to when it was administered without food. The median (range) Tmax for desvenlafaxine after administration of Desvenlafaxine fumarate ER with food was 7.75 (4.5 – 14.0) and 7.50 (4.5 – 14.0) when administered without food.

2.2.5 What are the general ADME (Absorption, Distribution, Metabolism and Elimination) Characteristics of Desvenlafaxine?

After administration of desvenlafaxine fumarate 50 mg ER tablet, the mean (%CV) elimination half-life (T ½) was 9.84 (14) hours which is similar to that observed after administration of Pristiq, 10.54 (27) hours. The median (range) time to peak concentration (Tmax) was 7.50 (4.50 – 14) hours.

Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. Approximately 45% of desvenlafaxine is excreted unchanged in urine at 72 hours after oral administration. Approximately 19% of the administered dose is excreted as the glucuronide metabolite and <5% as the oxidative metabolite (N,O-didesmethylvenlafaxine) in urine (Refer to Pristiq label for additional Pharmacokinetic information).

2.2.6 What is the composition of Desvenlafaxine base ER formulations used in the bioequivalence studies?

Tables 9 and 10 contain the qualitative and quantitative composition of Desvenlafaxine fumarate ER 50 and 100 mg tablets, respectively.

Table 9

Desvenlafaxine Fumarate E.R Tablets equivalent to 50mg Desvenlafaxine

Ingredient	Function	Amount (mg) / Tablet equivalent to 50mg Desvenlafaxine	Amount (%) / Tablet equivalent to 50mg Desvenlafaxine
Cores:			
Desvenlafaxine Fumarate (b) (4)	Drug substance	75.45	21.87
Microcrystalline Cellulose NF (b) (4)	(b) (4)		
Hypromellose USP (b) (4)			
Talc USP (b) (4)			
(b) (4)			
Purified Water USP q.s			
Magnesium Stearate NF (b) (4)			
Total:			(b) (4)

Table 10

Desvenlafaxine Fumarate E.R Tablets equivalent to 100mg Desvenlafaxine

Ingredient	Function	Amount (mg) / Tablet equivalent to 100mg Desvenlafaxine	Amount (%) / Tablet equivalent to 100mg Desvenlafaxine
Cores:			
Desvenlafaxine Fumarate (b) (4)	Drug substance	150.9	43.74
Microcrystalline Cellulose NF (b) (4)	(b) (4)		
Hypromellose USP (b) (4)			
Talc USP (b) (4)			
Purified Water USP q.s			
Magnesium Stearate NF (b) (4)			
Purified Water USP			
Total:			(b) (4)

2.3 Analytical Methods

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes, the active moiety, desvenlafaxine was appropriately measured in biological fluids.

What bioanalytical methods are used to assess concentrations of desvenlafaxine and is the validation complete and acceptable?

The concentrations of desvenlafaxine in human plasma were determined using a precise and accurate LC-MS/MS method. The calibration range of the method is 1 to 500 ng/mL. The method was sensitive, selective, accurate, and reproducible. O-desmethylvenlafaxine is stable during storage, processing and analysis in human plasma samples. The analytical method was adequately validated and acceptable.

The following is a tabular summary of the validation of the bioanalytical method.
Table 11: Summary of Analytical Method Validation

Matrix:		
	Type:	Human Plasma in K_2EDTA
	Volume:	0.200 mL
Concentrations:		
Lower limit of quantitation:		1.00 ng/mL
Concentration range:		1.00 ng/mL – 500 ng/mL
Concentrations of the QC samples:		
		LLOQ QC 1.00 ng/mL
		QC A 3.00 ng/mL
		QC B 200 ng/mL
		QC C 400 ng/mL
		QC D 800 ng/mL
Accuracy and Precision:		
LLOQ Intra-day:		
	Precision:	≤ 3.3 %
	Accuracy:	102.0 % to 107.0 %
LLOQ Inter-day:		
	Precision:	3.5 %
	Accuracy:	104.0 %
QC A, B, C Intra-day:		
	Precision:	≤ 3.3 %
	Accuracy:	96.0 % to 107.5 %
QC A, B, C Inter-day:		
	Precision:	≤ 3.0 %
	Accuracy:	98.5 % to 101.0 %
Correlation coefficients:		≥ 0.9997

Stability in human plasma:		
Freeze-thaw:	Four (4) cycles at -25 ± 10°C	
Bench top:	24.00 hours at room temperature	
Refrigerated:	23.50 hours at 5 ± 3°C	
Stability of processed samples:		
Autosampler:	96.25 hours at approximately 5°C	
Storage Stability:		
Reconstituted Samples:	99.75 hours at approximately 5°C	
Evaporated Samples:	4.00 hours at room temperature	
Stability in stock solutions:		
Short term:		
	Desvenlafaxine:	6.00 hours at room temperature
	Internal Standard:	6.00 hours at room temperature
Long term:		
	Desvenlafaxine:	13 days at 5 ± 3°C
Recovery:		
Desvenlafaxine:	101.5 % to 109.4 %	
Internal Standard:	102.4 %	
Dilution integrity:		
2-fold:	Precision:	1.4 %
	Accuracy:	102.5 %
5-fold:	Precision:	1.2 %
	Accuracy:	101.9 %
Selectivity:		Test met acceptance criteria
Concomitant medications in blank samples:		Test met acceptance criteria
Hormonal contraceptives in blank samples:		Test met acceptance criteria
Matrix effect:		
	Precision:	≤ 2.3 %
	Accuracy:	101.7 % to 102.8 %
Hemolyzed QC samples experiment:		
0.5 %	Precision:	≤ 3.6 %
	Accuracy:	101.0 % to 104.3 %
2.0 %	Precision:	≤ 2.6 %
	Accuracy:	100.5 % to 104.5 %

Appendices

3.1 OSI Report

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

DATE: September 12, 2013

TO: Mitchell Mathis, M.D., CAPT USPHS
Acting Director,
Division of Psychiatry Products
Office of New Drugs
Center for Drug Evaluation and Research

FROM: Jyoti B. Patel, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: **Review of EIR covering NDA 205208**, Desvenlafaxine Fumarate Extended-Release Tablets, sponsored by Teva Pharmaceuticals, USA

At the request of the Division of Psychiatry Products, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted audits of the clinical and analytical portions for the following bioequivalence studies.

1. Study Number: 53711

Study Title: "A pivotal, open-label, single-center, randomized, single-dose, two-period, two-treatment, two-sequence crossover study to compare the bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets 100 mg to Pristiq® Extended-Release Tablets, 100 mg under fasted conditions"

2. Study Number: **53811**

Study Title: "A pivotal, open-label, single-center, randomized, single-dose, two-period, two-treatment, two-sequence crossover study to compare the bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets 100 mg to Pristiq® Extended-Release Tablets, 100 mg under fed conditions"

3. Study Number: **2012-2883**

Study Title: "A single-dose, comparative bioavailability study of one formulation of Desvenlafaxine Fumarate Extended Release Tablets, equivalent to 50 mg Desvenlafaxine and one formulation of Pristiq® Extended Release Tablets, 50 mg under fasting and fed conditions"

The primary objective of these studies was to evaluate bioequivalence under fasted and fed conditions between desvenlafaxine fumarate extended release tablets (test) of Teva Pharmaceuticals, USA and Pristiq® extended release tablets (reference) of Wyeth Pharmaceuticals Inc., USA.

During June 26-July 3, 2013, ORA investigator, Brian R. Cronenwett from the Kansas City District Office, audited the clinical portions of studies 53711 and 53811 at QPS Bio-Kinetic Clinical Applications, Springfield, MO.

During (b)(4), ORA investigator, Susan D. Yuscius from the Chicago District Office, audited the clinical portion of study 2012-2883 and OSI scientist, (b)(4) audited the analytical portions of all three studies (53711, 53811, and 2012-2883) at (b)(4).

The audits included review of business organization, thorough examination of study records, facilities and equipment, interviews, and discussions with the firm's management and staff.

Following the inspections, Mr. Cronenwett issued a Form FDA-483 at QPS Bio-Kinetic Clinical Applications **(Attachment 1)** and Ms. Yuscius (b)(4) issued a Form FDA-483 at (b)(4) (b)(4) **(Attachment 4)**. DBGLPC received the firms' responses to the Form FDA-483s **(Attachments 2, 3, and 5)**. The

Form FDA-483 observations, firms' responses, and DBGLPC's evaluations of Form FDA-483 observations are discussed below:

QPS Bio-Kinetic Clinical Applications, Springfield, MO:

Clinical Portion: Form FDA-483 observations:

1. **Failure to report to the sponsor, adverse effect that may reasonably be regarded as caused by, or probably caused by, an investigational drug.**
   Specifically, an Adverse Event (A/E) the Principal Investigator (PI) designated as related to investigational product was not reported to the sponsor. Subject #26, (b)(6) (Alternate #3 pre-screen) (Study # 53711) reported an A/E "Headache" to a study monitor. The A/E was incorrectly captured on an inactive A/E raw data record, intended for another subject (b)(6) (#26 pre-screen), created to begin the screening process. Subject (b)(6), did not present to participate, and was documented as "No show" at screening/randomization and "not on study". The raw data A/E log for #26, (b)(6) was blank.

Response:
The firm sent a response on July 26, 2013 **(Attachment 2)** and a follow-up response on August 23, 2013 **(Attachment 3)**. In the responses, the firm agreed to the observation regarding the error in reporting the A/E for subject #26.

As a corrective action, the firm sent a 'Note to File' explaining the error to the sponsor, QPS Netherlands (Data Management), QPS Qualitix Taiwan (Biostatistics), and QPS Bioserve India (Report Writing). A letter detailing the missing A/E was also presented to the IRB at the July 22, 2013 meeting. An erratum was created as an addenda to the Clinical Study Report, which included the A/E of headache for subject #26 ((b)(6)). The erratum was submitted with the response date August 23, 2013.

To ensure integrity of the system, the firm implemented new SOPs and the employees have been trained. Also, the firm's QA Unit conducted a review of all the A/E reporting related to participant/subject movement for studies conducted in 2011, 2012, and 2013.

Evaluation:
DBGLPC reviewer is of the opinion that the firm's corrective actions are acceptable. The Review Division should note the

recording error of A/E for subject #26 ((b)(6)). This error is not likely to impact the overall data integrity of study 53711.

2. **Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation and informed consent. Specifically, for the following subjects, the raw data documented late draw due to "Difficult draw" and the eCRFs indicated the protocol deviation was attributed to "subject's late return to the clinic", which was reported to the sponsor. However, the subjects were actually "checked-in" to the site and under the firm's observation.**
   - **Subject #17, study 53711, Period 2 was documented in raw data as a late draw (11/20/2011, post-dose 6.0 hour data point)**
   - **Subject #18, study 53711, period 1 was documented in raw data as a late draw (11/30/2011, post-dose 7.5, and 14.0 hour data points)**

Response:
The firm sent a response on July 26, 2013 **(Attachment 2)** and a follow-up response on August 23, 2013 **(Attachment 3)**. In the response, the firm agreed to the observation regarding the incorrect records in CRFs.

As a corrective action, the firm's QA Unit conducted a review of all CRFs for study 53711. In addition to the errors discovered during the inspection, an additional error was discovered for a blood sampling time for subject #26, Period 1, 8.5 hours. The sample was taken at 14:55 on November 13, 2011, but it was reported in the CRF as 15:55. A "Note to file" explaining the error was sent to the sponsor, QPS Netherlands (Data Management), QPS Qualitix Taiwan (Biostatistics) and QPS Bioserve India (Report Writing). The IRB was notified of the error by the PI during the July 22, 2013 meeting.
The errata as addenda to the final Study Report with the deviations were submitted to the agency in the response on August 23, 2013 **(Attachment 3)**.

Evaluation:
DBGLPC reviewer is of the opinion that the firm's corrective actions are acceptable. The Review Division should note the recording errors in CRF. These errors are unlikely to impact the overall data integrity of study 53711 or human safety.

(b) (4)

Analytical portion: Form FDA-483 observations:

1. **For Validation study PMRI-1285-11 (Desvenlafaxine in human plasma) done to support of studies 2011-2749 (53711), 2011-2750 (53811), and 2012-2883: Failure to use freshly prepared calibrators to evaluate the stabilities of Desvenlafaxine. Specifically, freshly spiked calibration standards were not used to evaluate 'bench-top', 'refrigerated', 'freeze-thaw', and 'post-preparative' (autosampler/processed sample) stabilities of Desvenlafaxine.**

Response:
In the response dated August 21, 2013 **(Attachment 5)**, the firm acknowledged that freshly spiked calibration standards were not used for the above cited stability studies. However, the firm performed the 82-day long term stability at -25^{0}C using freshly spiked calibration standards. Also, in the response, the firm provided results of the re-evaluated bench-top, freeze-thaw, and post-preparative (refrigerated) stabilities of desvenafaxine using freshly spiked calibration standards.

Evaluation:
The firm's long term stability study (82 days) and revalidated stability studies performed using freshly spiked calibration standards are acceptable. With the provided information, this observation has no impact on the overall quality and integrity of the data for studies 53711, 53811, and 2012-2883.

2. **Failure to document all aspects of study conduct. Specifically, for study 2011-2749 (53711), unresolved interference peak was observed in the chromatograms of both periods for the following subjects (Attachment 6):**
   - **Subject 15 (analytical run: 2749-CR03-DEC0511RS)**
   - **Subject 34 (analytical run: 2749-CR07-DEC0611RS)**

A similar occurrence in a different study was addressed (Attachment 7); however, for study 2011-2749, the occurrence of the unresolved interference peak was not documented with proper justification.

Response:
In the response, the firm acknowledged that the presence of the interference peak in chromatograms of subject 15 and 34 should have been documented in the data. However, the firm did not perform any resolution of interference peak or impact analysis

of the interference peak for study 53711. Instead, during the FDA inspection, the firm excluded the data of subjects 15 and 34, and re-analyzed pharmacokinetic parameters for bioequivalence. The result showed that the two formulations are still bioequivalent **(Attachment 5)**.

Evaluation:
This reviewer is of the opinion that the firm should have resolved the interference peak and addressed its impact on accuracy of the sample analysis. In the absence of proper evaluation of impact of the interference peak observed in chromatograms of subjects 15 and 34, the accuracy of the sample analysis cannot be assured. DBGLPC reviewer recommends that subjects 15 and 34 should be excluded from the statistical data analysis and that the Review Division should verify the statistical analysis performed by the firm excluding subjects 15 and 34 **(Attachment 5)**.

Conclusion:

Following review and evaluation of the Form FDA-483 observations and the firms' responses, DBGLPC reviewer recommends that the **clinical and analytical data from studies 53711, 53811 and 2012-2883 are acceptable for further agency review with the following exceptions for study 53711.**

1. **The Review Division should take note of the discrepancy in reporting clinical data for subjects 17, 18 and 26.**
2. **For the analytical portion, subjects 15 and 34 should be excluded from the statistical data analysis.**

Jyoti B. Patel, Ph.D.
Pharmacologist
Bioequivalence Branch,
DBGLPC, OSI

Classification:

VAI: QPS Bio-Kinetic Clinical Applications, Springfield, MO
FEI: 1000511105
VAI: (b) (4)
FEI: (b) (4)

cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Patel/Choi/Dejernett/CF
HFC-130/ORA HQ OMPTO DMPTI MPTTPB BIMO
CDER/OND//DPP/Ansah, Kofi/Kumi, Kofi/Zhang, Jing/Mannheim, Glenn/Zhu, Hao/Mathis, Mitchell
HFR-SW350/Bromley, Gerald (DIB)/Lopicka, Warren (BIMO)/Cronenwett, Brian
Yuscius, Susan
Draft: JBP 9/09/2013
Edit: YMC 9/11/2013, WHT 9/12/2013
OSI file #: 6418; O:\BE\assigns\205208.pha.des.doc
ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB
FACTS: 1511883

ATTACHMENTS:

Attachment 1: Form FDA-483 (Bio-Kinetic Clinical Applications)
Attachment 2: Response 1 from Bio-Kinetic Clinical Applications
Attachment 3: Response 2 from Bio-Kinetic Clinical Applications
Attachment 4: Form FDA-483 (b) (4)
Attachment 5: Response from (b) (4)
Attachment 6: Interference peak observed for subjects 15 and 34 (Study 53711)
Attachment 7: Impact analysis for interference peak done in a different Desvenlafaxine study

3.2 Individual Reports

Biopharmaceutics

Report # 2012-2883	**Study Period**: 3/1/12 to 3/29/12	EDR Link: \\Cdsesub1\evsprod\nda205208\0000\m5

Title	A Single-Dose, Comparative Bioavailability Study of One Formulation of Desvenlafaxine Fumarate Extended Release Tablets, Equivalent to 50 mg Desvenlafaxine and One Formulation of Pristiq® Extended Release Tablets, 50 mg under Fasting and Fed Conditions
Objectives	The primary objective of this study is to evaluate the comparative bioavailability between Desvenlafaxine Fumarate (equivalent to 50 mg desvenlafaxine) Extended Release Tablets (Teva Pharmaceuticals USA) and Pristiq® 50 mg Extended Release Tablets (Wyeth Pharmaceuticals Inc., USA) after a single-dose in healthy subjects under fasting conditions. The secondary objective of this study is to evaluate the effect of food on Desvenlafaxine Fumarate (equivalent to 50 mg desvenlafaxine) Extended Release Tablets from Teva Pharmaceuticals USA after a single-dose in healthy subjects under fasting and fed conditions.

Study Design	
☑ Bioequivalence	☐ Bioavailability
Single-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy Vonuteers Six –sequence, three treatment	
Screening: ≤ 28 days	**Washout:** ≥ 7 days, outpatient
Period 1/2	34 hours, Inpatient stay ☑Y ☐ N:

Treatments: (Active Ingredient: Desvenlafaxine)

	Test	Reference
Dosage Form	Tablet	Tablet
Dosage Strength	50 mg	50 mg
Batch #.	K-46726	E99239
Administration	Oral	Oral

Treatment

Treatment A: One tablet Desvenlafaxine fumarate 50 mg (Teva) ER administered after an overnight fast of at least 10 hours

Treatment B: One tablet of Desvenlafaxine fumarate 50 mg (Teva) administered 30 minutes after the start of a high fat, high calorie breakfast

Treatment C: One tablet of Pristiq 50 mg ER tablets (Wyeth) administered after an overnight fast of at least 10 hours

Breakfast Menu

	CALORIES (kcal)	TOTAL FAT (g)	CARBOHYDRATES (g)	PROTEIN (g)
• 2 eggs	140	10	0	12
• 10 g of butter for cooking eggs	70	8	0	0
• 2 slices of toast	229	3	42	7
• 10 g of butter for toast	70	8	0	0
• 113 g of hash brown potatoes	239	12	31	3
• 250 mL of whole milk	160	8	12	8
• 2 slices of bacon	89	7	0	6
TOTAL WEIGHT (g)		**56**	**85**	**36**
TOTAL CALORIES (kcal)		**504**	**340**	**144**
RELATIVE CALORIC CONTENT		**50.6%**	**34.1%**	**14.4%**

Sampling Times (PK, plasma)

- Test: 0, 1.5, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 16, 18, 24, 36, 48, 60 hours post dose
- Reference: 0, 1.5, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 16, 18, 24, 36, 48, 60 hours post dose

Analytical Method:
. LC/MS/MS. The analytical method used for the study is the same as the validated method.

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	30/28/2
Age [Median (range)]	41 ± 10 (22 -55) years
Male/Female	12/18
Race (Caucasian/Black/Asian/other)	20/2/3/5

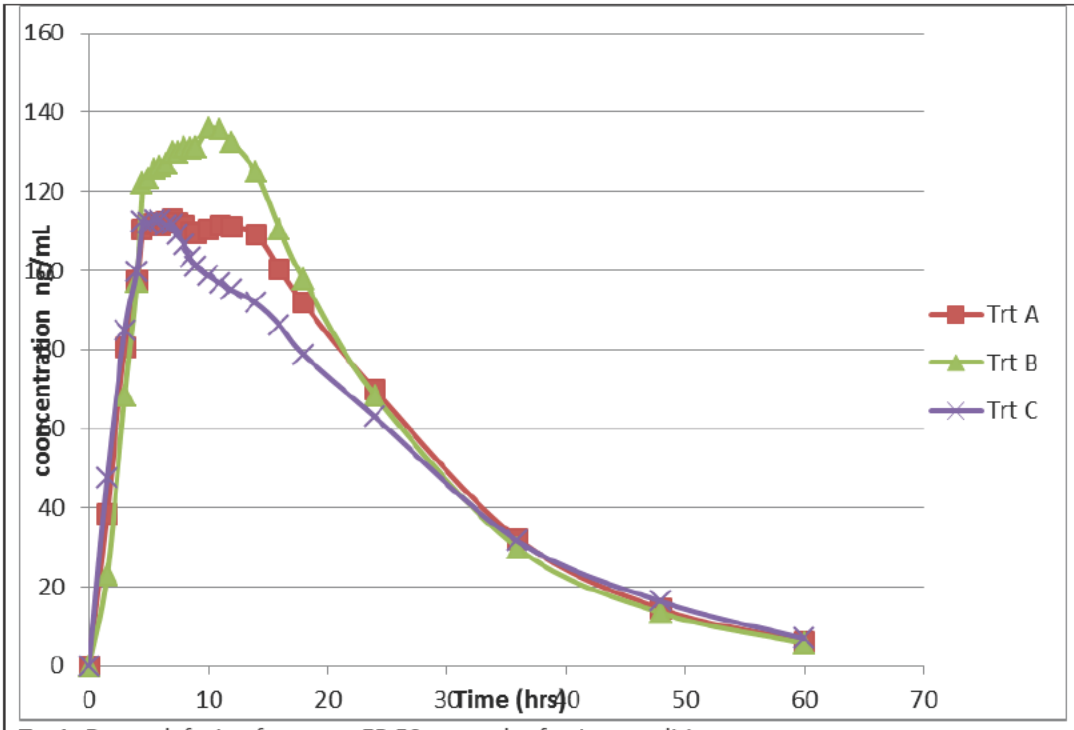
Results

Summary of Pharmacokinetic Parameters with Statistical Evaluation

Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
Cmax	**A**	28	131.35 (29)	126.15	**A vs C**	109.96	102.70 - 117.73	15
(ng/mL)	**B**	28	154.14 (24)	150.16	**B vs A**	119.03	111.27 - 127.33	15
	C	27	120.36 (32)	114.73				
AUCt	**A**	28	3188.93 (35)	3002.61	**A vs C**	107.63	101.01 - 114.69	14
(ng.h/mL)	**B**	28	3342.32 (28)	3230.47	**B vs A**	107.59	101.05 - 114.55	14
	C	27	2999.63 (33)	2789.71				
AUCinf	**A**	28	3282.36 (36)	3080.93	**A vs C**	106.73	100.05 - 113.86	14
(ng.h/mL)	**B**	28	3429.74 (29)	3308.07	**B vs A**	107.37	100.73 - 114.45	14
	C	27	3124.79 (36)	2886.64				
Tmax	**A**	28	8.46 (44)					
(h)	**B**	28	8.25 (37)					
	C	27	7.72 (54)					
kel	**A**	28	0.0717 (13)					
(1/h)	**B**	28	0.0729 (14)					
	C	27	0.0692 (19)					
Thalf	**A**	28	9.84 (14)					
(h)	**B**	28	9.71 (16)					
	C	27	10.54 (27)					
			Median	***Range***				
Tmax	**A**	28	7.50	4.50-14.00				
(h)	**B**	28	7.75	4.50-14.00				
	C	27	6.00	4.00-16.00				

Trt A: Desvenlafaxine ER 50 mg (Fasting), Trt B: Desvenlafaxine ER 50 mg (fed), Trt C: Pristig 500 mg ER (Fasting)

Mean plasma desvenlafaxine concentration time profile after administration of 50 mg Desvenlafaxine fumarate ER and Pristiq ER



Trt A: Desvenlafaxine fumarate ER 50 mg under fasting conditions
Trt B: Desvenlafaxine fumarate ER 50 mg with food
Trt C: Pristiq ER 50 mg under fasting conditions

Site Inspected	
Requested: Yes☑ No ☐	**Performed:** Yes☑ No ☐ N/A ☐

Safety

The sponsor reported that no death or serious AEs were reported during the conduct of this study. Subject 15 (female, 32 years, White) was dismissed from the study after Period 1 dosing due to an AE. The AE consisted of vomiting and was judged as mild in severity. The AE resolved with no action taken, and was judged to have reasonable possibility to the study drug. Subject 15 (female, 32 years, White) was dismissed from the study after Period 1 dosing due to an AE. The AE consisted of vomiting and was judged as mild in severity. The AE resolved with no action taken, and was judged to have reasonable possibility to the study drug.

Conclusion

The 90% confidence intervals of the relative mean AUCt, AUCinf and Cmax of the test to reference products under fast condition are within the 80-125% bioequivalence range. Hence, Desvenlafaxine fumarate 50 mg (Teva) is bioequivalent to Pristiq. Food increases the peak systemic exposure (Cmax) by ~19% compared to the fasting state. The upper limit of the 90% confidence interval is just above the 125.00% upper limit of the bioequivalence range (127.33%). The statistical results show that the total systemic exposure (AUCt and AUCinf) is ~7-8% higher under fed conditions compared to drug administration in the fasting state.

Comments

The reviewer agrees with the Sponsor's conclusions. The median Tmax is about 1.5 hours longer after administration Desvenlafaxine fumarate ER compared to Pristiq ER under fasting conditions. The difference is not expected to be clinically relevant.

Biopharmaceutics-

Report # 53711	Study Period: November 2011	EDR Link: \\Cdsesub1\evsprod\nda205208\0000\m5

Title	A Pivotal, Open-Label, Single-Center, Randomized, Single-Dose, Two-Period, Two-Treatment, Two-Sequence Crossover Study to Compare the Bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets 100 mg to Pristiq® Extended-Release Tablets, 100 mg Under Fasted Conditions
Objectives	The primary objective of this pivotal study was to assess the bioequivalence of Teva Pharmaceutical's Desvenlafaxine Fumarate ER Tablets, 100 mg to Wyeth Pharmaceuticals Inc.'s Pristiq® ER Tablets, 100 mg, under fasted conditions.

Study Design

☑ Bioequivalence	☑ Bioavailability

Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers

Screening: ≤ 28 days	**Washout:** ≥ 7 days, outpatient
Period 1/2	36 hours , Inpatient stay ☑Y ☐ N:

Treatments: (Active Ingredient: Desvenlafaxine)

	Test	Reference
Dosage Form	Tablet	Tablet
Dosage Strength	100 mg	100 mg
Batch #.	K-46406	E-12613
Administration	Oral	Oral

Treatment A: One tablet of Teva's Desvenlafaxine Fumarate ER tablet, 100 mg
Treatment B: One tablet of Wyeth Pharmaceutical Inc's Pristiq 100 mg ER tablet

Sampling Times (PK, plasma)

- Test: pre-dose (0), 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 24, 36, 48, 60 hours post dose
- Reference: 0, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 24, 36, 48, 60 hours post dose

Analytical Method: The performance of the analytical method is acceptable. Yes ☑ No ☐
LC/MS/MS. Range was from 1 to 500 ng/mL. Inter-day precision and accuracy of the calibration standards ranged from 0.6 % to 2.2 % and 98.5 % to 101.0 % respectively. Intra-day precision and accuracy of the quality control samples ranged from 0.3 % to 5.3 % and 93.2 % to 105.5 % respectively. Inter-day precision and accuracy ranged from 2.3 % to 3.3 % and 96.4 % to 101.5 % respectively.

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

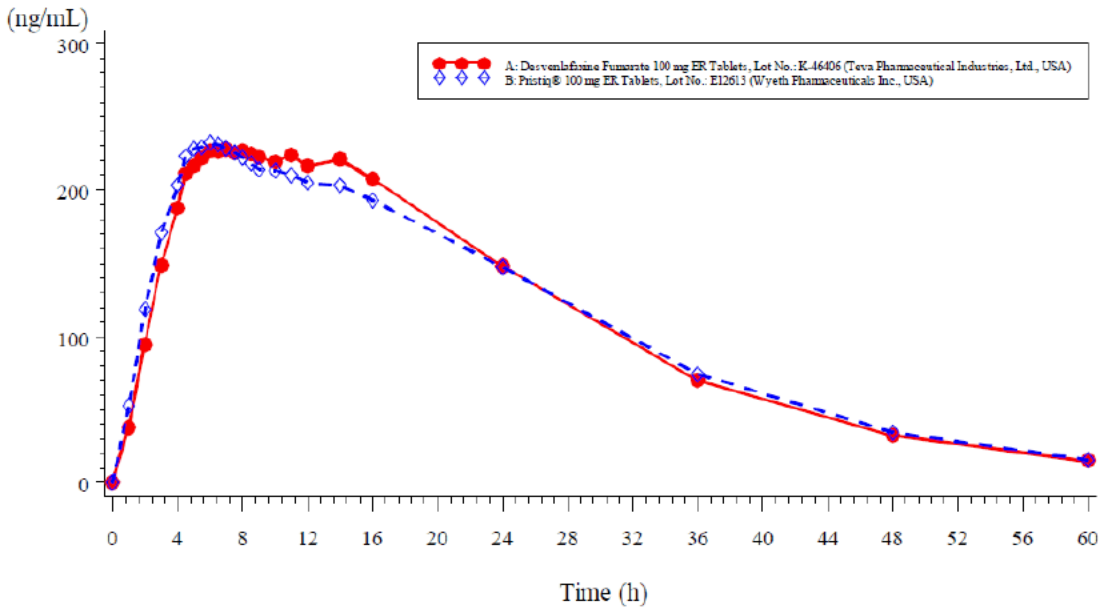
Study Population :

Randomized/Completed/ Discontinued Due to AE	34/27/6 (emesis)
Age [Median (range)]	40.6 ± 15.0 years (20 – 75) years
Male/Female	12/22

	Race (Caucasian/Black/Asian/other)	29/4/0/1	

Results

Mean Plasma Concentration versus Time Profiles



Summary of Desvenlafaxine Pharmacokinetic Parameters after a Single Dose of Treatments A or B to Healthy Subjects under Fasting Conditions

Parameter	Treatment A (n=27)		Treatment B (n=27)	
	Arithmetic Mean	CV%	Arithmetic Mean	CV%
C_{max}(ng/mL)	249.26	32	247.93	30
AUC_{0-t} (h•ng/mL)	6644.04	32	6648.86	24
AUC_{0-inf} (h•ng/mL)	6897.50	33	6926.35	26
T_{max}*(h)	8.00(4.50-16.00)		6.50 (4.50-16.00)	
$t_{1/2}$ (h)	10.33	18	10.98	22
λ_z (hr^{-1})	0.0690	17	0.0655	18

AM: Arithmetic Mean; CV: Coefficient Variation=SD/AM ; NA: Not Applicable
GM: Geometric Mean; n: number of subjects
Treatment A: Desvenlafaxine Fumarate ER Tablets, 100 mg, Test Formulation
Treatment B: Pristiq® ER Tablets, 100 mg, Reference (Wyeth Pharmaceuticals Inc.)
*: Expressed as median (range)

Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Treatments A or B to Healthy Subjects under Fasting Conditions (N=27)

Parameter	Least Squares Geometric Mean		Ratio of Geometric Mean (%)	90% Confidence Interval (%)
	Treatment A	Treatment B	A/B	A/B
C_{max} (ng/mL)	237.68	237.97	99.88	91.56 - 108.95
AUC_{0-t} (h•ng/mL)	6244.12	6430.71	97.10	88.58 - 106.44
AUC_{0-inf} (h•ng/mL)	6451.54	6675.01	96.65	88.12 - 106.01
Treatment A: Desvenlafaxine Fumarate ER Tablets, 100 mg, Test Formulation A Treatment B: Pristiq® ER Tablets, 100 mg, Reference				

Site Inspected

Requested: Yes☑ No ☐ | **Performed:** Yes☑ No ☐ N/A ☐

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

The sponsor reported that in general Desvenlafaxine fumarate ER tablet, 100 mg was well tolerated in this study. The sponsor reported that 24 subjects reported 62 adverse events of mild to moderate intensity including; 11 adverse events of headache, 21 adverse events of nausea, 8 adverse events of emesis, 4 adverse event of diarrhea, 2 adverse events each of dry mouth, restlessness, lightheaded, and 1 adverse event each of difficulty concentration, loss of appetite, somnolence, restless in legs, syncope, fever, stomach pain, shakiness, disorientation, anorexia, dizziness and, soreness in left hand.

Conclusion

The results from this study demonstrated that Teva Pharmaceutical's Desvenlafaxine Fumarate ER Tablets, 100 mg (Treatment A) were bioequivalent to Wyeth Pharmaceuticals Inc.'s Pristiq® ER Tablet, 100 mg (Treatment B) with respect to C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for Desvenlafaxine after administration of single doses of 100 mg desvenlafaxine fumarate ER tablets under fasting conditions.

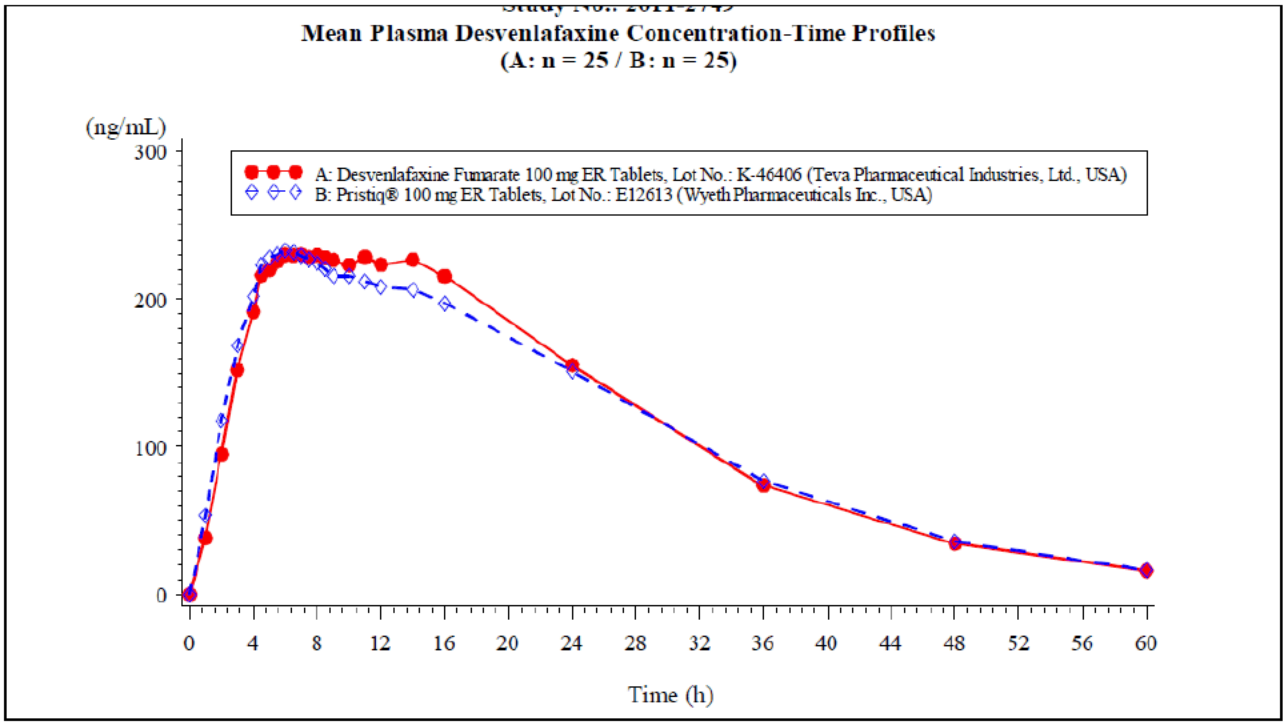
Comments

The reviewer agrees with the sponsor's conclusion. The median Tmax was about 1.5 hours longer after administration of Desvenlafaxine fumarate ER compared to Pristiq ER. The Office of scientific investigations (OSI) inspection revealed that there were problems with the analytical runs for subjects 15 and 34. Therefore, OSI recommended that the data for these subjects be excluded from the data set and the statistical analysis re-done. The results of the re-calculated data are provided below. The results of the recalculated are consistent with the conclusions that Desvenlafaxine fumarate ER (Teva) is bioequivalent to Pristiq ER 100 mg under fasting conditions.

Summary of Study Results Based on Plasma Desvenlafaxine Levels
Subjects 15, 34 Excluded

Based on Raw Data								
Parameter	***Trt***	***n***	***Arithmetic Mean (CV%)***	***Geometric Mean***	***Contrast***	***Ratio (%)***	***90% Confidence Interval***	***Intra-Sbj CV(%)***
Cmax	**A**	25	253.24 (32)	242.72	**A vs B**	101.10	92.14 - 110.94	19
(ng/mL)	**B**	25	249.24 (30)	240.07				
AUCt	**A**	25	6878.36 (29)	6568.43	**A vs B**	99.25	90.39 - 108.97	19
(ng·h/mL)	**B**	25	6773.86 (23)	6618.37				
AUCinf	**A**	25	7148.58 (31)	6801.73	**A vs B**	98.76	89.88 - 108.51	20
(ng·h/mL)	**B**	25	7066.98 (24)	6887.11				
Kel	**A**	25	0.0681 (17)					
(h)	**B**	25	0.0646 (19)					
Thalf	**A**	25	10.47 (18)					
(h)	**B**	25	11.15 (21)					
			Median	***Range***				
Tmax	**A**	25	8.00	4.50-16.00				
(h)	**B**	25	6.50	4.50-16.00				

Treatment A (Test)	*Desvenlafaxine Fumarate 100 mg ER Tablets, Lot No.: K-46406 (Teva Pharmaceutical Industries, Ltd., USA)*
Treatment B (Ref)	*Pristiq® 100 mg ER Tablets, Lot No.: E12613 (Wyeth Pharmaceuticals Inc., USA)*



Biopharmaceutics

Report # 53811	**Study Period**: Not Available	EDR Link: \\Cdsesub1\evsprod\nda205208\0000\m5
Title	A Pivotal, Open-Label, Single-Center, Randomized, Single-Dose, Two-Period, Two-Treatment, Two-Sequence Crossover Study to Compare the Bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets 100 mg to Pristiq® Extended-Release Tablets, 100 mg Under Fed Conditions	
Objectives	The primary objective of this pivotal study was to assess the bioequivalence of Teva Pharmaceutical's Desvenlafaxine Fumarate ER Tablets, 100 mg to Wyeth Pharmaceuticals Inc.'s Pristiq® ER Tablets, 100 mg, under fed conditions.	
Study Design		
☑ Bioequivalence	☑ Bioavailability	
Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers		
Screening: ≤ 28 days	**Washout:** ≥ 7 days, outpatient	
Period 1/2	34 hours, Inpatient stay ☑Y ☐ N:	

Treatments: (Active Ingredient: Desvenlafaxine)

	Test	Reference
Dosage Form	Tablet	Tablet
Dosage Strength	100 mg	100 mg

	Batch #.	K-46406	E-12613
	Administration	Oral	Oral

Treatment A: Desvenlafaxine Fumarate ER Tablets, 100 mg, Test Formulation administered 30 minutes after start of meal
Treatment B: Pristiq® ER Tablets, 100 mg, Reference, administered 30 minutes after start of meal

The meal consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk (or equivalent substitutions providing a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume, density, and viscosity).

Sampling Times (PK, plasma)

- Test: pre-dose (0), 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 24, 36, 48, 60 hours post dose
- Reference: 0, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 24, 36, 48, 60 hours post dose

Analytical Method: The performance of the analytical method is acceptable. Yes ☑ No ☐
LC/MS/MS. Range was from 1 to 500 ng/mL. Inter-day precision and accuracy of the calibration standards ranged from 0.4 % to 3.3 % and 99.3 % to 101.0 % respectively. Intra-day precision and accuracy of the quality control samples ranged from 0.2 % to 6.1 % and 93.0 % to 104.7 % respectively. Inter-day precision and accuracy ranged from 2.3 % to 5.0 % and 96.3 % to 101.3 % respectively.

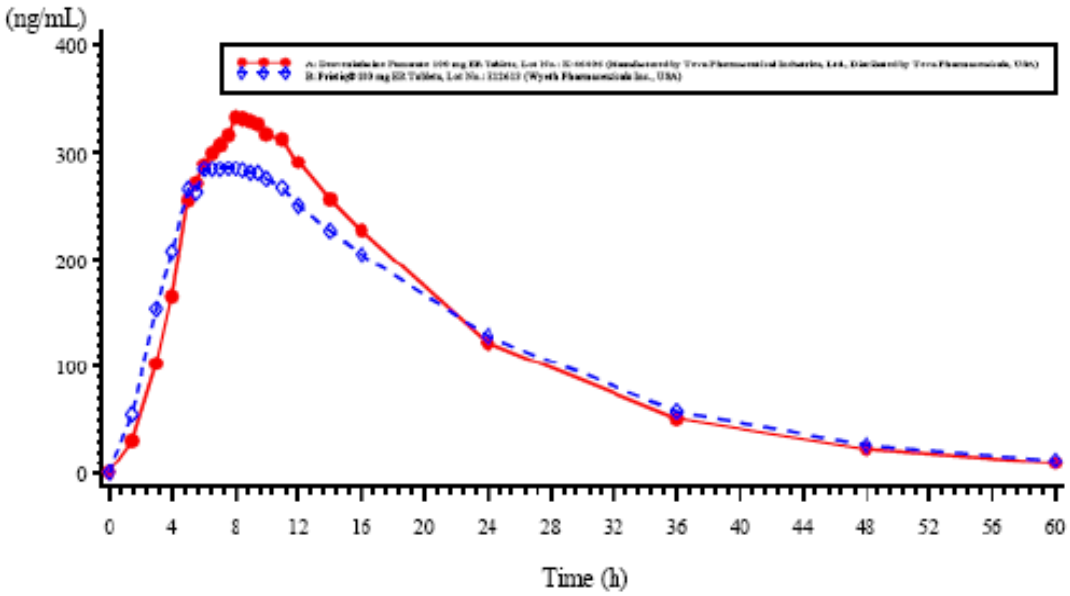
Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	24/22/2 (emesis)
Age [Median (range)]	37.3 ± 15.6 (20 – 75) years
Male/Female	11/13
Race (Caucasian/Black/Asian/other)	21/2/0/1

Results

Mean Plasma Concentration versus Time Profiles



Summary of Desvenlafaxine Pharmacokinetic Parameters after a Single Dose of Treatments A or B to Healthy Subjects under Fed Conditions

	Treatment A (n=22)		Treatment B (n=22)	
Parameter	Arithmetic Mean	CV%	Arithmetic Mean	CV%
C_{max}(ng/mL)	379.64	28	326.73	18
AUC_{0-t} (h•ng/mL)	6713.66	17	6609.53	17
AUC_{0-inf} (h•ng/mL)	6865.18	17	6807.94	17
T_{max}*(h)	8.00 (5.00-16.00)		7.00 (5.00-11.00)	
$T_{1/2}$ (h)	9.43	19	10.29	24
λz (hr^{-1})	0.0760	19	0.0709	24

AM: Arithmetic Mean; CV: Coefficient Variation=SD/AM ; NA: Not Applicable
GM: Geometric Mean; n: number of subjects
Treatment A: Desvenlafaxine Fumarate ER Tablets, 100 mg, Test Formulation
Treatment B: Pristiq® ER Tablets, 100 mg, Reference (Wyeth Pharmaceuticals Inc.)
*: Expressed as median (range)

Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Treatments A or B to Healthy Subjects under Fed Conditions (N=27)

Parameter	Least Squares Geometric Mean		Ratio of Geometric Mean(%)	90% Confidence Interval(%)
	Treatment A	Treatment B	A/B	A/B
C_{max} (ng/mL)	361.03	320.18	112.76	105.04- 121.05
AUC_{0-t} (h•ng/mL)	6613.93	6509.42	101.61	98.96- 104.32
AUC_{0-inf} (h•ng/mL)	6766.91	6700.88	100.99	98.27- 103.78

Treatment A: Desvenlafaxine Fumarate ER Tablets, 100 mg, Test Formulation A
Treatment B: Pristiq® ER Tablets, 100 mg, Reference

Site Inspected

Requested: Yes☑ No ☐ | **Performed:** Yes☑ No ☐ N/A ☐

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

The sponsor reported that 12 subjects reported 33 adverse events of mild intensity including; 7 adverse events of headache, 11 adverse events of nausea, 3 adverse events of anxiety, 2 adverse events each of visual disturbance and 1 adverse event each of emesis, diarrhea, dizziness, stomach cramps, bilateral jaw paresthesia, diaphoresis, trembling in legs (bilateral), weakness in legs (bilateral), blurred vision and swelling in right eye.

Conclusion

The results from this study demonstrated that Teva Pharmaceutical's Desvenlafaxine Fumarate ER Tablets, 100 mg (Treatment A) were bioequivalent to Wyeth Pharmaceuticals Inc.'s Pristiq® ER Tablet, 100 mg (Treatment B) with respect to Cmax, AUC0-t, and AUC0-∞ for Desvenlafaxine after administration of single doses of 100 mg desvenlafaxine fumarate ER tablets under fed conditions.

Comments

The reviewer agrees with the sponsor's conclusion. The median Tmax for desvenlafaxine after administration Desvenlafaxine fumarate ER 1 hour longer than after administration of Pristiq ER. This difference is not expected to be clinically relevant.

Bioanalytical Report

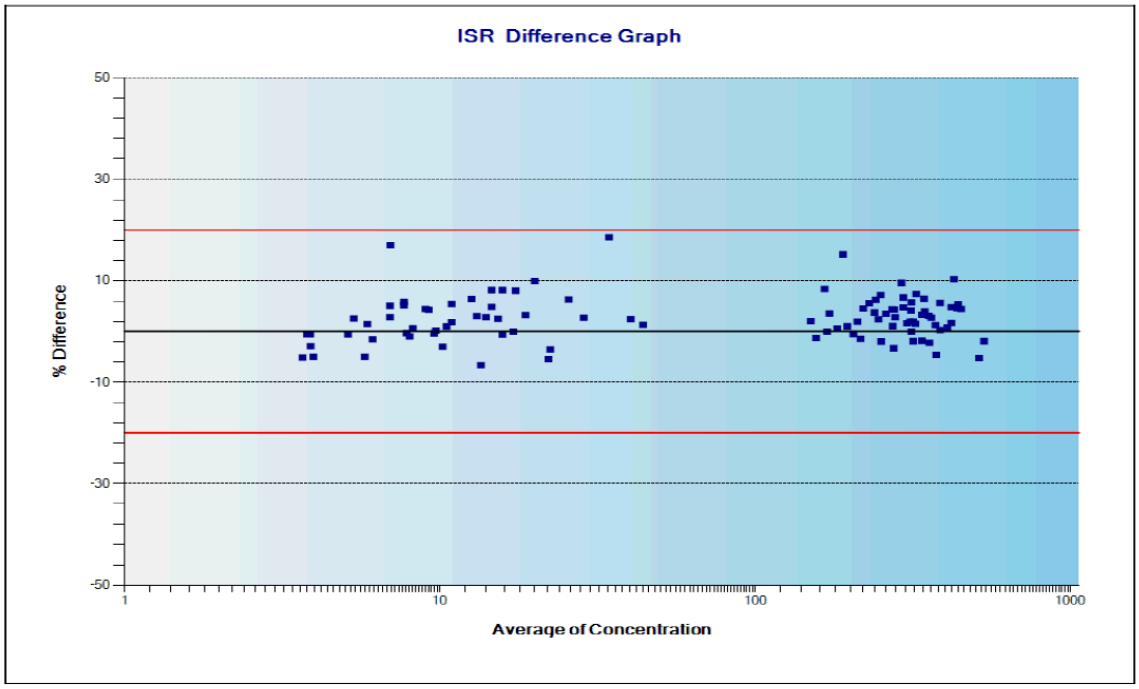
A liquid chromatographic tandem mass spectrometric method for the determination of desvenlafaxine in human plasma was developed and validated. The method involved liquid-liquid extraction and has demonstrated the following performance characteristics:

Matrix:		
	Type:	Human Plasma in K_2EDTA
	Volume:	0.200 mL
Concentrations:		
Lower limit of quantitation:		1.00 ng/mL
Concentration range:		1.00 ng/mL – 500 ng/mL
Concentrations of the QC samples:		
		LLOQ QC 1.00 ng/mL
		QC A 3.00 ng/mL
		QC B 200 ng/mL
		QC C 400 ng/mL
		QC D 800 ng/mL
Accuracy and Precision:		
LLOQ Intra-day:		
	Precision:	≤ 3.3 %
	Accuracy:	102.0 % to 107.0 %
LLOQ Inter-day:		
	Precision:	3.5 %
	Accuracy:	104.0 %
QC A, B, C Intra-day:		
	Precision:	≤ 3.3 %
	Accuracy:	96.0 % to 107.5 %
QC A, B, C Inter-day:		
	Precision:	≤ 3.0 %
	Accuracy:	98.5 % to 101.0 %
Correlation coefficients:		≥ 0.9997

Stability in human plasma:			
Freeze-thaw:	Four (4) cycles at -25 ± 10°C		
Bench top:	24.00 hours at room temperature		
Refrigerated:	23.50 hours at 5 ± 3°C		
Stability of processed samples:			
Autosampler:	96.25 hours at approximately 5°C		
Storage Stability:			
Reconstituted Samples:	99.75 hours at approximately 5°C		
Evaporated Samples:	4.00 hours at room temperature		
Stability in stock solutions:			
Short term:			
	Desvenlafaxine:	6.00 hours at room temperature	
	Internal Standard:	6.00 hours at room temperature	
Long term:			
	Desvenlafaxine:	13 days at 5 ± 3°C	
Recovery:			
Desvenlafaxine:	101.5 % to 109.4 %		
Internal Standard:	102.4 %		
Dilution integrity:			
2-fold:	Precision:	1.4 %	
	Accuracy:	102.5 %	
5-fold:	Precision:	1.2 %	
	Accuracy:	101.9 %	
Selectivity:		Test met acceptance criteria	
Concomitant medications in blank samples:		Test met acceptance criteria	
Hormonal contraceptives in blank samples:		Test met acceptance criteria	
Matrix effect:			
	Precision:	≤ 2.3 %	
	Accuracy:	101.7 % to 102.8 %	
Hemolyzed QC samples experiment:			
0.5 %	Precision:	≤ 3.6 %	
	Accuracy:	101.0 % to 104.3 %	
2.0 %	Precision:	≤ 2.6 %	
	Accuracy:	100.5 % to 104.5 %	

Lipemic QC samples experiment:		
	Precision:	≤ 3.8 %
	Accuracy:	100.4 % to 104.5 %
Evaluation in the presence of concomitant medications:		
	% Difference:	-1.5 % to 1.6 %
Evaluation in the presence of hormonal contraceptives:		
	% Difference:	-2.3 % to 1.2 %

Graphical Representation of Incurred Sample Reanalysis for Desvenlafaxine



Conclusion: The analytical method for the determination of desvenlafaxine in human plasma was shown to be specific, sensitive, linear, precise, accurate and reproductive. The analytical method and validation is acceptable.

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/s/

KOFI A KUMI
09/20/2013

HAO ZHU
09/20/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205-208	**Reviewer:** Banu S. Zolnik, Ph.D.	
Division:	Division of Psychiatry Products		
Applicant:	Teva Pharmaceutical USA	**Biopharmaceutics Secondary Signature:** Sandra Suarez-Sharp, Ph.D.	
Trade Name:	N/A	**Biopharmaceutics Supervisory Lead (acting)**: Richard Lostritto, Ph.D.	
Generic Name:	Desvenlafaxine Fumarate	**Date Assigned:**	January 10, 2013
Indication	It is indicated for the treatment of major depressive disorder.	**Date of Review:**	September 4, 2013
Formulation/ Strength	Extended Release Tablets, Eq. to 50 mg & 100 mg base	**Route of Administration**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	**Date of informal/Formal Consult**	**Primary Review due in DARRTS**
December 12, 2012 March 26, 2013 Sequence 002 September 4, 2013 Sequence 007	NA	September 5, 2013
Type of Submission:	505 (b) (2)	
Review Key Points:	▪ Dissolution method and acceptance criteria ▪ In vitro alcohol dose dumping studies	

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

In NDA 205-208, Teva Pharmaceutical USA seeks approval to market Desvenlafaxine Extended Release (ER) Tablets for the treatment of major depressive disorder. The proposed commercial strengths of desvenlafaxine ER tablets are 50 mg and 100 mg. (b) (4)

The development program supporting this submission consists of the following three bioequivalence studies: Two BE fasting and fed studies following single dose administration comparing Desvenlafaxine Fumarate ER Tablets Eq. to 100 mg to the RLD, Pristiq® ER Eq. to 100 mg Tablets and a single dose cross-over BE study comparing Desvenlafaxine Fumarate ER Tablets Eq. to 50 mg to Pristiq® ER, Eq to 50 mg under fasting and fed conditions. All the PK studies are being reviewed by OCP.

This review evaluates and makes recommendations on the acceptability of the dissolution method and acceptance criteria and the *in vitro* alcohol dose dumping studies for Desvenlafaxine Fumarate ER Tablets, 50 mg and 100 mg.

1) DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

The following dissolution method and acceptance criteria for Desvenlafaxine have been agreed upon with the Applicant and are deemed acceptable. The Applicant accepted the FDA-recommended dissolution acceptance criteria during a teleconference dated September 3, 2013 and made a commitment to send the updated specification sheet reflecting the changes by September 9, 2013.

USP Apparatus	Agitation Speed	Medium	Temperature	Volume	Agreed upon Acceptance Criteria for Desvenlafaxine Fumarate ER Tablets 50 mg and 100 mg
I (basket)	100 rpm	0.05 M Acetate Buffer, pH 4.5	37°C ± 0.5 °C	900 mL	1 hour: NMT (b) (4) %
					8 hour: (b) (4) %
					12 hour: (b) (4) %
					24 hour: NLT (b) (4) %

Summary of dissolution method development for 50 mg strength

The Applicant formulated experimental batches of Desvenlafaxine ER, 50 mg by varying amounts of the rate (b) (4) conducted bioequivalence studies with these formulations at a scale-up batch. The (b) (4) batch failed to show bioequivalence against the RLD while the (b) (4) batch was bioequivalent to the RLD. Dissolution profiles of these formulations were similar with f2 values >50 indicating that the original dissolution method (USP I basket, 100 rpm, (b) (4) (b) (4) 900 mL) was failing to reject the bioinequivalent batch. During the review cycle, ONDQA-Biopharmaceutics review team discussed the lack of discriminating ability of the dissolution method with the Applicant. The Applicant proposed revising the dissolution method to USP I basket, 100 rpm, 0.05 M Acetate Buffer, pH 4.5, 900 mL to increase its discriminating ability. However, ONDQA-Biopharmaceutics team informed the Applicant that the revised dissolution method in pH 4.5 marginally rejects the failed batch and recommended to tighten the acceptance criteria to increase the discriminating ability. With the revised method and acceptance criteria summarized in the above table the discriminating ability of the method is increased.

Summary of dissolution method development for 100 mg strength

The Applicant formulated three pilot bio batches of Desvenlafaxine ER, 100 mg by varying the ratio of the rate (b) (4) conducted bioequivalence studies with these formulations. The results of the bioequivalence studies failed to show bioequivalence against RLD for batches K-45978, and K-45979, while batch K-45963 was shown to be bioequivalent to RLD. However, the original proposed dissolution method failed to reject bioinequivalent batch of K-45979. Following the discussion with the Applicant about the lack of discriminatory ability of the dissolution method, the Applicant conducted cross-study statistical analysis and concluded that batches K-45979 and K-45963 were considered bioequivalent to each other, and while batches K-45978 and K-45963 were not bioequivalent to each other. With this information, it is concluded that the original dissolution method and acceptance criteria is adequate to discriminate the failed BE batches. Although the original dissolution method was adequate for 100 mg strength, the Applicant proposed the revised dissolution method mentioned above (USP I basket, 100 rpm, 0.05 M Acetate Buffer, pH 4.5, 900 mL) for 100 mg strength as well. The revised dissolution method is found acceptable by the ONDQA-Biopharmaceutics review team since the dissolution profiles are overlapping in both dissolution method conditions.

2) EVALUATON OF THE IN VITRO ALCOHOL DOSE DUMPING STUDIES

The Applicant provided dissolution data conducted using the originally proposed QC media and 0.1 N HCl with alcohol concentration at 0%, 5%, 10%, 20% and 40%. In vitro alcohol dose dumping studies for both strengths did not indicate any dose dumping in presence of alcohol.

RECOMMENDATION:
The ONDQA/Biopharmaceutics team has reviewed NDA 205-208 and its amendments submitted on March 26, 2013 and September 4, 2013. The following dissolution method and dissolution acceptance criteria for Desvenlafaxine Fumarate Extended Release Tablets, 50 mg, and 100 mg have been agreed upon with the Applicant (refer to submission dated September 4, 2013):

USP Apparatus	Agitation Speed	Medium	Temperature	Volume	Agreed upon Acceptance Criteria for Desvenlafaxine Fumarate ER Tablets 50 mg and 100 mg
I (basket)	100 rpm	0.05 M Acetate Buffer, pH 4.5	37°C ± 0.5 °C	900 mL	1 hour: NMT (b) (4) % 8 hour: (b) (4) % 12 hour: (b) (4) % 24 hour: NLT (b) (4) %

From the Biopharmaceutics perspective, NDA 205-208 for Desvenlafaxine Fumarate Extended Release Tablets, 50 mg, and 100 mg is recommended for APPROVAL.

Banu S. Zolnik, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez-Sharp, Ph. D.
Biopharmaceutics Secondary Signature
Office of New Drug Quality Assessment

cc: R Lostritto

BIOPHARMACEUTICS ASSESSMENT

1. BACKGROUND

Submission:

Desvenlafaxine is a selective serotonin and norepinephrine reuptake inhibitor and is indicated for the treatment of major depressive disorder. The Applicant is seeking approval to market Desvenlafaxine (b) (4) Extended Release Tablets, 50 mg and 100 mg.

The Applicant submitted this 505 (b) (2) Application to rely on the Agency's finding of the safety and effectiveness of the previously approved drug product, Pristiq® ER Eq. 50 mg and 100 mg base (desvenlafaxine succinate, NDA 21-992, approval date February 29, 2008). Desvenlafaxine Fumarate ER Tablets 50 mg and 100 mg (b) (4). The applicant conducted BE studies on both strengths.

The development program supporting this submission consists of the following three bioequivalence studies: Two BE fasting and fed studies of single dose two treatment two-period, two-sequence crossover study comparing Desvenlafaxine Fumarate ER Tablets Eq. to 100 mg to the RLD, Pristiq® ER Eq. to 100 mg Tablets. Another single dose cross-over study comparing Desvenlafaxine Fumarate ER Tablets Eq. to 50 mg to Pristiq® ER, Eq. to 50 mg was conducted under fasting and fed conditions by including a fed arm to determine the food effect. All the PK studies are being reviewed by OCP.

Review: The Biopharmaceutics review is focused on the acceptability of the dissolution method and acceptance criteria and on the evaluation of in vitro alcohol dose dumping studies.

Drug Substance

The applicant provided solubility of desvenlafaxine fumarate in various solvents in the table below.

Table 1: Solubility of desvenlafaxine fumarate

Solvent	Concentration	Classification
water	1mg/ml	slightly soluble
n-hexane	<0.1mg/ml	practically insoluble
toluene	<0.1mg/ml	practically insoluble
ethanol	1mg/ml	slightly soluble
acetone	0.1mg/ml	very slightly soluble
dichloromethane	<0.1mg/ml	practically insoluble

pH	Solubilty (mg/ml)	Parts of Solvent Required for 1 Part of Solute	Expressed as USP Solubility
1.0	61.8	16	Soluble
4.5	8.2	122	Slightly Soluble
6.8	12.4	81	Sparingly Soluble

Reviewer's Comments

The concentration of higher strength (100 mg) desvenlafaxine in the dissolution media of 900 mL is 0.11 mg/mL, and solubility of desvenlafaxine fumarate in water is 61.8 mg/mL, which is approximately 561 times more of the desvenlafaxine concentration, therefore, sink conditions are achieved in the original dissolution media.

The concentration of higher strength (100 mg) desvenlafaxine in the revised dissolution media of pH 4.5 Acetate Buffer in 900 mL is 0.11 mg/mL, and solubility of desvenlafaxine fumarate in pH 4.5 is 8.2 mg/mL, which is approximately 74 times more of the desvenlafaxine concentration, therefore, sink conditions are achieved in the revised dissolution media.

Drug Product

The drug formulation is an extended release tablet. Table 2 below shows the composition for both strengths 50 mg and 100 mg strengths. (b) (4)

Table 2. Components and Quantitative Composition of Desvenlafaxine Fumarate ER Tablets, 50 mg, and 100 mg

Ingredient	Amount (mg) / Tablet		Amount (%) / Tablet	
	Eq. to 50 mg base	Eq. to 100 mg base	Eq. to 50 mg base	Eq. to 100 mg base
Cores				
Desvenlafaxine Fumarate (b) (4)	75.45	150.9	21.87	43.74
Microcrystalline Cellulose NF (b) (4)	(b) (4)			
Hypromellose USP (b) (4)				
Talc USP (b) (4)				
Purified Water USP				
Magnesium Stearate NF (b) (4)				
(b) (4)				
Total				

(b) (4)

Reviewer's Comments

As noted above, the two formulations (b) (4). The Applicant is not requesting a biowaiver because the Applicant submitted bioequivalence studies on both strengths. The assessment of the BE studies are found in the Clinical Pharmacology Review.

2. DISSOLUTION METHOD

Dissolution testing is performed at release and on stability. The original dissolution method being proposed for Desvenlafaxine Extended Release Tablets, 50 and 100 mg is summarized below:

The Applicant's Original Proposed Dissolution Method				
USP Apparatus	**Agitation Speed**	**Medium**	**Temperature**	**Volume**
I (basket)	100 rpm	(b) (4)	37°C ± 0.5 °C	900 mL
Sampling times: 1, 4, 8, 12 and 24 hours				

Reviewer's Comment:
During the review cycle and upon the FDA's request, the Applicant proposed the revised dissolution method below for both strengths to increase the discriminatory ability of the method for 50 mg strength. As stated in the later sections of this review, the revised dissolution method is found acceptable for both strengths.

The Applicant's Revised Dissolution Method				
USP Apparatus	**Agitation Speed**	**Medium**	**Temperature**	**Volume**
I (basket)	100 rpm	0.05 M Acetate Buffer, pH 4.5	37°C ± 0.5 °C	900 mL
Sampling times: 1, 8, 12 and 24 hours				

The Applicant utilized risk assessment approach to identify and evaluate the formulation variables and drug manufacturing process that can impact drug product critical quality attributes (CQA) and dissolution was found to be a CQA (Table 3).

Table 3: Risk Assessment of Formulation Variables

Table 18: Initial Risk assessment of the Formulation Variables

	Formulation Variables				
DP CQA	(b) (4)	Amount	Amount	Talc Amount	Magnesium Stearate Amount
Assay	Low	Low	Low	Low	Low
Impurities	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low	Low
Dissolution	High	High	Medium	Low	Low

Relative Risk Ranking:
Low risk: no further investigation is needed.
Medium risk: further investigation may be needed.
High risk: further investigation is needed

(b) (4) grade and amount, and (b) (4) amount were identified as the high and medium risk variables that can affect dissolution. Therefore, the Applicant investigated the use of low, high, and combination of low and high viscosity grades of (b) (4). Different amounts of low viscosity (b) (4) showed similar dissolution profiles but with higher release rate as compared to that of the RLD (Pristiq) therefore, the Applicant did not pursue low viscosity (b) (4) in their formulation. (b) (4)

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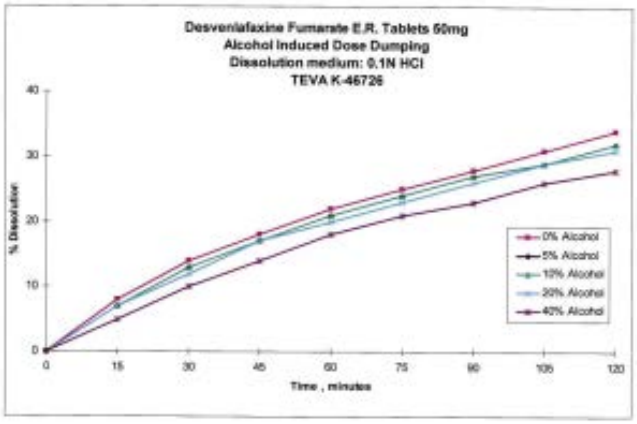
(b) (4)

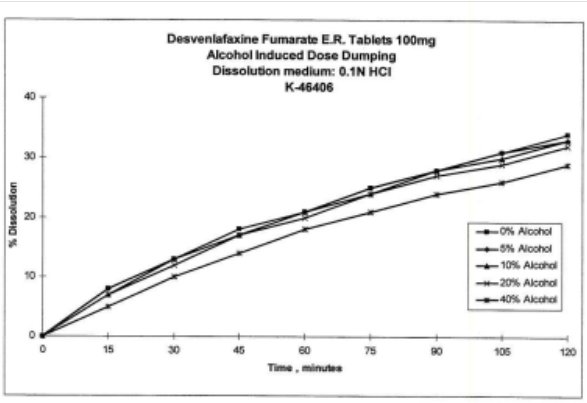
4. EVALUATION OF IN VITRO ALCOHOL INDUCED DOSE DUMPING

The Applicant provided dissolution data conducted using the proposed QC media, and 0.1 N HCl with alcohol concentration at 0%, 5%, 10%, 20% and 40% and calculated f2 values between the dissolution profiles using 0% alcohol as the reference per FDA's comments provided during the IND phase[1].



f2 values for K-46726 in 0.1N HCl*	
5% Alcohol:	90
10% Alcohol:	90
20% Alcohol:	82
40% Alcohol:	67

* 0% Alcohol is used as reference



f2 values for K-46406 in 0.1N HCl*	
5% Alcohol:	97
10% Alcohol:	96
20% Alcohol:	90
40% Alcohol:	71

* 0% Alcohol is used as reference

Figures 7-8: In vitro alcohol induced dose dumping dissolution profiles of 50 mg strength (left) and 100 mg strength (right) t (Figure is pasted from Original Submission 5.4 dose dumping dissolution report for k46726 and 46406.pdf

Reviewer's Comment

In vitro alcohol dose dumping studies for both strengths did not indicate any dose dumping in presence of alcohol.

[1] Pre-IND 113-629 comments dated 12/01/2011 entered DARRTS by Juliette T. Toure.

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

/s/

BANU S ZOLNIK
09/04/2013

SANDRA SUAREZ
09/04/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**205208**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**I**	**Generic Name**	**Desvenlafaxine fumarate**
Medical Division	DPP	**Drug Class**	**SNRI**
OCP Reviewer	**Kofi Kumi**	**Indication(s)**	**Treatment of Major Depressive Disorder**
OCP Team Leader	**Hao Zhu**	**Dosage Form**	**Extended Release Tablets (50mg and 100 mg)**
Pharmacometrics Reviewer		**Dosing Regimen**	**50 mg daily**
Date of Submission	**12/12/12**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**9/13/13**	**Sponsor**	**Teva Pharmaceuticals**
Medical Division Due Date	**9/21/13**	**Priority Classification**	**Standard**
PDUFA Due Date	**10/13/13**		

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Summary

The sponsor has developed a desvenlafaxine fumarate extended release tablets and is seeking approval via the 505(b)(2) route. The sponsor is cross referencing Pristiq (Desvenlafaxine Succinate) by Wyeth, which is approved for major depressive disorder. The dosing in MDD for Pristiq is 50 mg daily. The sponsor has developed a 50 and 100 mg ER tablets. Pristiq is also available in 50 mg and 100 mg ER tablets. Clinical studies for Pristiq were conducted using doses from 50 to 400 mg tablets. There is no clinical advantage of the higher doses over the 50 mg dose.

The NDA is dependent on three bioequivalent studies:

Study Number 53711: A Pivotal, Open-Label, Single-Center, Randomized, Single-Dose, Two-Period, Two-Treatment, Two-Sequence Crossover Study to Compare the Bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets 100 mg to Pristiq® Extended-Release Tablets, 100 mg Under Fasted Conditions

Study Number 53811: A Pivotal, Open-Label, Single-Center, Randomized, Single-Dose, Two-Period, Two-Treatment, Two-Sequence Crossover Study to Compare the Bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets 100 mg to Pristiq® Extended-Release Tablets, 100 mg Under Fed Conditions

Study Number 2012-2883: A Single-Dose, Comparative Bioavailability Study of One Formulation of Desvenlafaxine Fumarate Extended Release Tablets, Equivalent to 50 mg Desvenlafaxine and One Formulation of Pristiq® Extended Release Tablets, 50 mg under Fasting and Fed Conditions

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	**505 (b)(2)**			
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**	**3**		
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**	**3**		
I. Clinical Pharmacology	**x**			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**x**			
Healthy Volunteers-				
single dose:	**x**	**3**		
multiple dose:				
Patients-				

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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**	**3**		
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	**x**	**1**		
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**4**		

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?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	the analytical assay?				
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 legible so that a substantive review can begin?	x			
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?
___Yes_____

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

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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

Reviewing Clinical Pharmacologist	Kofi Kumi, Ph.D.	Date 1/4/13
Team Leader/Supervisor	Hao Zhu, Ph.D.	Date

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

/s/

KOFI A KUMI
02/01/2013

HAO ZHU
02/01/2013