# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 205583Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

**Clinical Pharmacology Review**

| | |
|---|---|
| NDA: | 205583 |
| 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: | SUN Pharma Global FZE |
| | |
| Submission Type: | Original NDA [505(b)(2)] |
| Priority Classification: | Standard |
| Submission Date: | 3/25/13 |
| | |
| OCP Division: | DCP1 |
| OND Division: | DPP |
| | |
| Reviewer: | Kofi Kumi, Ph.D. |
| Team Leader: | Hao Zhu, Ph.D. |

## Table of Contents


Executive Summary ..... 3
1.1 Recommendation ..... 3
1.2 Post Market Studies ..... 3
1.3 Labeling Recommendations ..... 3
1.4 Summary of Clinical Pharmacology and Biopharmaceutics ..... 4
2. Question Based Review (QBR) ..... 8
2.1 General Attributes ..... 8
*2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?* ..... 8
*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?* ..... 8
*2.1.3 What are the proposed mechanism (s) of action and therapeutic indication(s)?* ..... 9
*2.1.4 What are the proposed dosage and route of administration?* ..... 9
*2.1.4 What is the reported adverse event profile from the bioequivalence studies?* ..... 9
*2.1.5 Is it acceptable for Desvenlafaxine fumarate ER tablet to be administered with food?* ..... 10
2.2 General Clinical Pharmacology and Biopharmaceutics ..... 12
*2.2.1 What are the design features of the clinical pharmacology and/or bopharmaceutics studies used to support dosing or claims?* ..... 12
*2.2.2 Is Desvenlafaxine Fumarate 100 mg ER bioequivalent to the reference listed drug, Pristiq (desvenlafaxine succinate) 100 mg ER under fasting conditions?* ..... 13
*2.2.3 Is Desvenlafaxine fumarate (SUN) 50 mg ER tablet bioequivalent to the reference listed drug, Pristiq® (desvenlafaxine succinate) 50 mg ER under fasting conditions?* ..... 15
*2.2.4 Is the exposure to Desvenlafaxine fumarate significantly different after administration of Desvenlafaxine fumarate 100 mg with or without food?* ..... 16

*2.2.5. How does the exposure to desvenlafaxine after administration of Desvenlafaxine fumarate ER with food compare to exposure after administration of Pristiq under fasting conditions?* ..... 17
*2.2.6 What are the general ADME (Absorption, Distribution, Metabolism and Elimination) Characteristics of Desvenlafaxine?* ..... 19
*2.2.7 What is the composition of Desvenlafaxine fumarate ER formulations used in the bioequivalence studies?* ..... 19
2.3 Analytical Methods ..... 20
*2.3.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?* ..... 20
*2.3.2. What bioanalytical methods are used to assess concentrations of desvenlafaxine and is the validation complete and acceptable?* ..... 20
3. Appendix ..... 21
3.1. Individual Studies ..... 21
3.2. OSI Report (Refer to OSI report) ..... 33

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 under fasting conditions.
- Desvenlafaxine fumarate ER can be administered with or without food.
- Desvenlafaxine fumarate ER exhibits extended release characteristics similar to the approved Pristiq ER, as supported by its *in vivo* pharmacokinetic profile.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) supports a recommendation for approval of Desvenlafaxine fumarate ER (SUN Pharma) 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 10 hours. The median (range) time to peak concentration (Tmax) is 6.0 (3.0 – 16.0) hours after administration of 50 mg desvenlafaxine fumarate extended release tablet*

*A food-effect study involving administration of Desvenlafaxine fumarate extended-release 100mg 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 37% in the fed state, while the AUC was increased by about 29%. Tmax was increased by about 2.5 hours after administration with food. These differences in Cmax, AUC and Tmax are not expected to be clinically significant. 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 by SUN Pharma was demonstrated to be bioequivalent to Pristiq® (Desvenlafaxine succinate) ER Tablet under fasting at 50 mg and 100 mg strengths, respectively. Tables 1 to 2 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. The 90% confidence intervals (CI) of the mean ratios for both Cmax and AUC fall within the regulatory criteria of 80% to 125% to declare the products are bioequivalent. Therefore, Desvenlafaxine fumarate ER is bioequivalent to Pristiq ER tablet, the reference drug, under fasting conditions.

The median Tmax of desvenlafaxine after administration of Desvenlafaxine fumarate ER was 1 hour longer than that after administration of Pristiq ER. The difference is not expected to be clinically relevant. 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.

When Desvenlafaxine fumarate ER 100 mg tablet (SUN) was administered under fed conditions compared to when given under fasting conditions, Cmax increased by about 37% and AUC by about 29% (Table 3 and 4). The increase in Cmax and AUC were significant. 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.
Figure 1contains plasma concentration time profile for Desvenlafaxine fumarate ER 100 mg (SUN) under fed and fasting conditions and Pristiq ER under fasting conditions.

Figure 1: Mean Plasma Desvenlafaxine Concentration Time Profile after Administration of 100 mg Desvenlafaxine fumarate ER and Pristiq ER

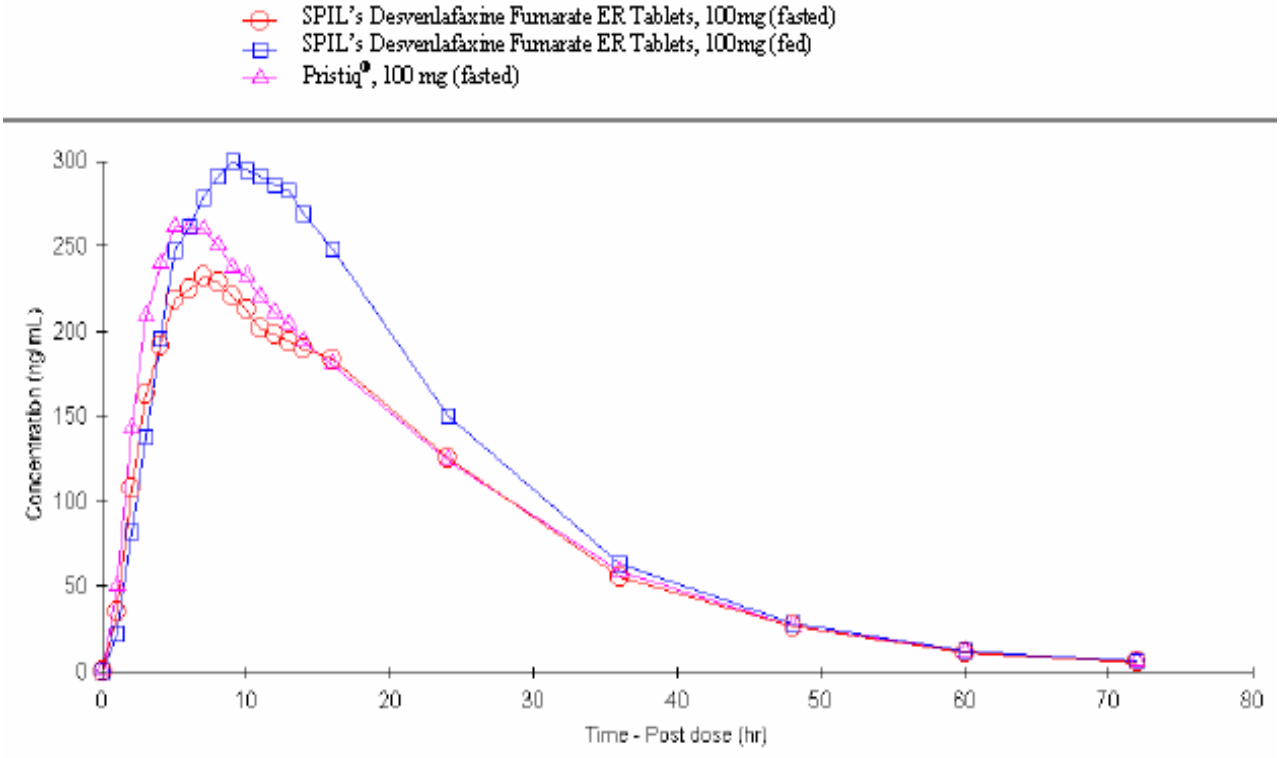



Table 1: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Desvenlafaxine fumarate ER (SUN) or Pristiq 100 mg to Healthy Subjects under Fasting Conditions (N=33)

| Parameter | Geometric Mean | | Ratio of Least Square (LS) Mean (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Treatment A (n=33) | Treatment C (n=33) | A/C | |
| Cmax (ng/mL) | 243.02 | 272.23 | 89.27 | 83.66 – 95.25 |
| AUCt (ng*hr/mL) | 5353.99 | 5994.04 | 89.32 | 80.96 – 98.55 |
| AUC∞ (ng*hr/mL) | 5433.11 | 6077.98 | 89.39 | 80.98 – 98.67 |
| Tmax [hr]* | 7.00 (3 – 16) | 6.00 (3 – 12) | | |
| T ½ [hr]# | 10.04 (1.32) | 10.13 (1.54) | | |

*Median (range); Mean# (SD)
Trt A: Desvenlafaxine fumarate ER 100 mg under fasting conditions
Trt C: Pristiq ER 100 mg under fasting conditions

Table 2: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Desvenlafaxine fumarate ER (SUN) and Pristiq ER 50 mg to Healthy Subjects under Fasting Conditions (N=47)

| Parameter | Geometric Mean | | Ratio of LS Mean (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Treatment A | Treatment B | A/B | |
| Cmax (ng/mL) | 114.05 | 124.17 | 91.86 | 87.71 – 96.20 |
| AUCt (ng*hr/mL) | 2507.46 | 2777.99 | 90.26 | 81.62 – 99.82 |
| AUC∞ (ng*hr/mL) | 2551.09 | 2829.92 | 90.15 | 81.58 – 99.61 |
| Tmax [hr][*] | 6.0 (3.0 – 16.0) | 5.0 (3.0 – 12.0) | | |
| T ½ [hr][#] | 9.6 (1.7) | 9.9 (2.0) | | |

[*]Median (range); Mean[#] (SD)
Trt A: Desvenlafaxine fumarate ER 50 mg under fasting conditions
Trt B: Pristiq ER 50mg under fasting conditions

Table 3: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Desvenlafaxine fumarate ER (SUN) 100 mg to Healthy Subjects under Fed or Fasting Conditions (N=33)

| Parameter | Geometric Mean | | Ratio of LS Mean (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Treatment A (n=33) | Treatment B (n=33) | B/A | |
| Cmax (ng/mL) | 243.02 | 332.93 | 136.99 | 127.65 – 146.11 |
| AUCt (ng*hr/mL) | 5353.99 | 6955.14 | 129.32 | 115.90 – 144.29 |
| AUC∞ (ng*hr/mL) | 5433.11 | 7039.71 | 129.57 | 115.62 – 143.89 |
| Tmax [hr][*] | 7.00 (3 – 16) | 9.50 (4 – 16) | | |
| T ½ [hr][#] | 10.04 (1.32) | 9.98 (1.26) | | |

[*]Median (range); Mean[#] (SD)
Trt A: Desvenlafaxine fumarate ER 100 mg under fasting conditions
Trt B: Desvenlafaxine fumarate ER 100 mg under fed conditions

Table 4: Summary of Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after Administration Desvenlafaxine fumarate ER (SUN) with Food and Pristiq ER 100 mg without Food

| Parameter | Geometric Mean | | Ratio of Mean (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Treatment B (n=33) | Treatment C (n=33) | B/C | |
| Cmax (ng/mL) | 332.63 | 271.70 | 122.43 | 115.03 – 130.29 |
| AUCt (ng*hr/mL) | 6963.70 | 5961.82 | 116.80 | 107.75 – 126.62 |
| AUC∞ (ng*hr/mL) | 7047.88 | 6045.28 | 116.58 | 107.51 – 126.43 |
| Tmax [hr][*] | 9.5 (4.0 – 16.0) | 6.0 (3.0 -12.0) | | |
| T ½ [hr][#] | 9.98 (1.25) | 10.13 (1.54) | | |

[*]Median (range); Mean[#] (SD)
Trt B: Desvenlafaxine fumarate ER 100 mg with food
Trt C: Pristiq ER 100 mg under fasting conditions

When you compare Desvenlafaxine fumarate ER administered under fed conditions with Pristiq ER administered under fasting conditions, Cmax increased by about 22% and AUC increased by about 17%. The increase in Cmax and AUC observed when Desvenlafaxine fumarate ER (SUN) given with food compared to Pristiq administered without food is lower than that seen when Desvenlafaxine fumarate ER (SUN) is compared to itself administered with or without food. Also, Cmax and AUC are about 10% lower when Desvenlafaxine fumarate ER (SUN) is given without food compared to when Pristiq ER is given without food (Tables 1 and 2). Therefore administering Desvenlafaxine fumarate ER (SUN) with food minimizes the difference in exposure (Cmax and AUC) observed when compared to Pristiq ER administered with or without food.

The sponsor reported that, in the food effect study for Desvenlafaxine fumarate ER, despite the increase in Cmax and AUC with food, the most common adverse events were seen frequently when Desvenlafaxine fumarate ER was administered under fasting not fed conditions (Refer to medical review for Agency's assessment). The increase in exposure due to administration with food does not appear to translate into an increase in adverse events. It is not expected that the increase in exposure (Cmax and AUC) after administration Desvenlafaxine fumarate ER with food would result in a substantially different adverse event profile from that seen with the reference drug, Pristiq.

It is stated in the Pristiq label that Desvenlafaxine causes sustained hypertension in a dose dependent manner. The increase in exposure observed with food is not expected to cause increases in blood pressure that are clinically different from that observed when Pristiq ER is administered based on the established dose-response relationship for sustained hypertension. In addition, the label also recommends that blood pressure should be monitored on a regular basis when patients are on Desvenlafaxine ER tablets. Either dose reduction or discontinuation should be considered if sustained increase in blood pressure is observed. Therefore, it is acceptable for Desvenlafaxine fumarate ER to be administered with or without food.

*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 and sites were inspected by the Office of Scientific Investigations (OSI). OSI inspection report is pending. In preliminary communication, the OSI inspector indicated that no issues that would affect a recommendation of approval of the NDA were identified (Refer to OSI report).

2. Question Based Review (QBR)

2.1 General Attributes

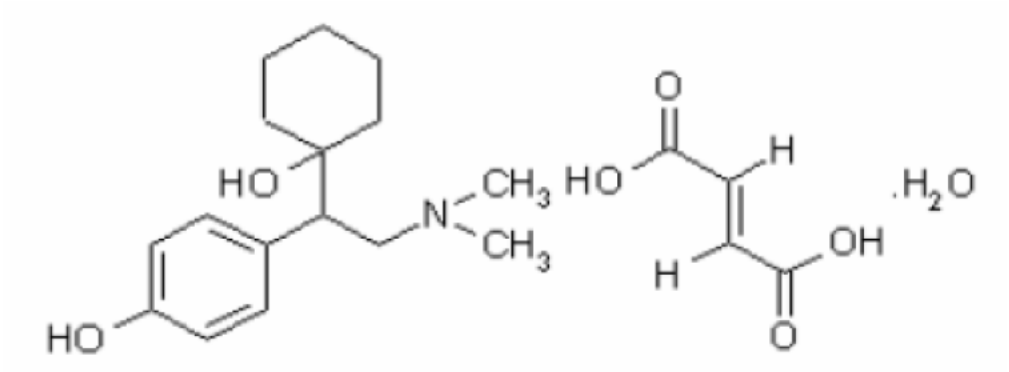
*2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?*

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 proposed indication, dose, route, and duration of administration of Sun Pharma Global FZE's Desvenlafaxine Extended-Release Tablets will be the same as those of the reference product, Pristiq. The application was primarily based on demonstration of bioequivalence between Desvenlafaxine fumarate ER (SUN) and Pristiq and determination of the food effect on the test 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 (b) (4) powder that is slightly soluble in water. Its chemical name is (±)-4-[2-dimethylamino-1-(1-hydroxycycohexyl)-ethyl]-phenol fumarate monohydrate (salt). The chemical structure is presented in Figure 2.

Figure 2: Structure of Desvenlafaxine Fumarate




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. The sponsor states that the drug product utilizes a (b) (4)

(b) (4)

*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.

*2.1.4 What is the reported adverse event profile from the bioequivalence studies?*

In the pivotal bioequivalence study for the Desvenlafaxine ER 100 mg tablets, the sponsor reported that out of 9 adverse events, 7 (77.8%) adverse events were experienced by 3 (8.6%) subjects when received treatment A (Desvenlafaxine ER 100 mg under fasting conditions) and all these 3 subjects were dropped due to adverse event. 1 (11.1%) adverse event was experienced by 1 (2.9%) subject who received treatment C (Pristiq ER 100 mg under fasting conditions) and dropped from the study due to adverse event. Remaining 1 (11.1% of 9) adverse event which was considered to have emerged from all three treatments occurred in 1subject. No death occurred

during the study. Most common adverse event reported was diarrhea which occurred on 4 occasions, 3 times with the treatment A and 1 time with treatment C. The sponsor reported that there was no significant difference between safety profiles of all three treatments.
The sponsor reported that for the bioequivalence study evaluating Desvenlafaxine ER 50 mg tablets, 3 subjects' experienced 3 post dose adverse events. Out of 3 adverse events, 1 (33.3%) adverse event was experienced by 1 subject who received treatment A and was dropped from the study. Remaining 2 (66.7 %) adverse events were experienced by 2 subjects who received treatment B and both these subjects were dropped from the study. The adverse event in the patient in Treatment A was vomiting. One subject in Treatment B experienced diarrhea and the other musculoskeletal pain. Refer to medical review for Agency's evaluation of safety.

*2.1.5 Is it acceptable for Desvenlafaxine fumarate ER tablet to be administered with food?*

It is acceptable that Desvenlafaxine fumarate ER tablet is administered with or without food.

When Desvenlafaxine fumarate ER 100 mg tablet (SUN) was administered under fed conditions compared to when given under fasting conditions, Cmax increased by about 37% and AUC by about 29%. The increase in Cmax and AUC were significant. When you compare Desvenlafaxine fumarate ER administered under fed conditions with Pristiq ER administered under fasting conditions, Cmax increased by about 22% and AUC increased by about 17%. In the approved label for Pristiq, when it was administered under fed compared to fasting conditions, Cmax is reported to increase by about 16% with no significant increase in AUC.

The sponsor reported that despite the increase in Cmax and AUC observed when administered with food, the most common adverse events were seen frequently when Desvenlafaxine fumarate ER was administered under fasting compared to fed conditions (Table 5) (Refer to medical review for Agency assessment). The increase in exposure due to administering with food does not appear to translate into an increase in adverse events. It must be noted that the number of subjects evaluated under fasting conditions were about twice as many as that under fed conditions. Desvenlafaxine exposures (Cmax and AUC) were about 10% lower after administration with Desvenlafaxine fumarate ER (SUN) compared to Pristiq ER under fasting conditions. It is not expected that the increase in exposure (Cmax and AUC) after administration Desvenlafaxine fumarate ER with food would result in a substantially different adverse event profile from that seen with the reference drug, Pristiq.

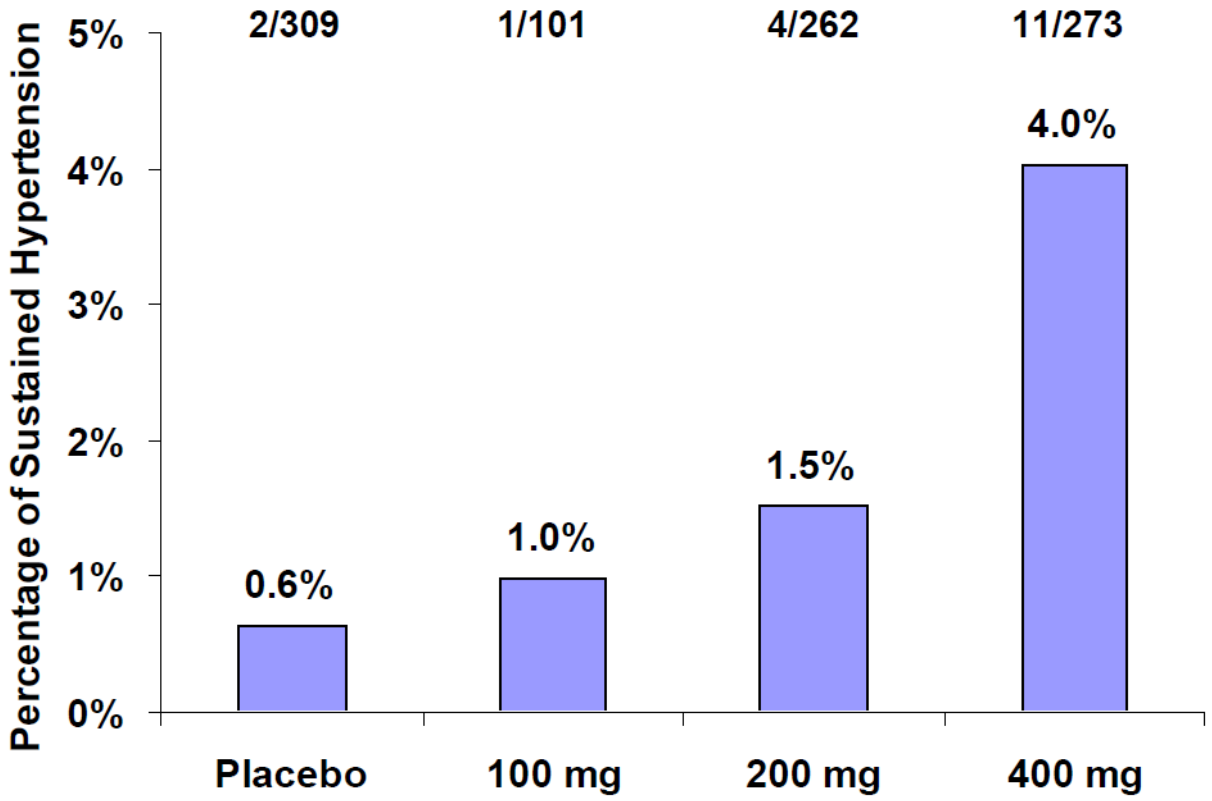
Table 5: Non-Laboratory Treatment Emergent Adverse Events by Dosing Condition after administration Desvenlafaxine fumarate ER (Sponsor's analysis)

| Preferred term | N (%) | |
|---|---|---|
| | Fasted (N=147) | Fed (N=71) |
| Diarrhea | 9 (6.1%) | 0 |
| Dizziness | 1 (<1%) | 0 |
| Dyspepsia | 1 (<1%) | 0 |
| Groin pain | 0 | 1 (1.4%) |
| Nausea | 2 (1.4%) | 1 (1.4%) |
| Somnolence | 1 (<1%) | 0 |
| Vomiting | 2 (1.4%) | 0 |

Source: Sponsor's safety summary

In the original OCP review of Pristiq (Desvenlafaxine succinate) ER, it was noted that Desvenlafaxine causes sustained hypertension in a dose dependent manner. OCP analysis indicated that the percentage of patients with sustained hypertension was 0.6%, 1% and 1.5% for patients who were administered placebo, 100 mg and 200mg Pristiq ER, respectively. The recommended desvenlafaxine dose is 50 mg. The 37% increase in exposure after administration of 50 mg Desvenlafxine fumarate ER (SUN) with food would yield limited increase in the incidence of sustained hypertension (approximate 0.1%) for patients receiving Desvenlafaxine fumarate consistently under fed condition versus under fast condition. Approximately 6% (across trial comparison) higher desvenlafaxine exposure is anticipated in patients receiving Desvenlafaxine fumarate ER as compared to receiving Pristiq, both under fed conditions. The difference in exposure is not expected to cause increases in blood pressure that are clinically different from that observed when Pristiq ER is administered. In addition, the label recommends that blood pressure should be monitored on a regular basis when patients are on Desvenlafaxine ER tablets. Either dose reduction or discontinuation should be considered if sustained increase in blood pressure is observed. Therefore, it is acceptable for Desvenlafaxine fumarate ER to be administered with or without food.

Figure 3: Dose Dependent Sustained Hypertension
(OCP analysis)




Source: OCP review of Pristiq (NDA 21992)

*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 pivotal bioequivalence studies comparing Desvenlafaxine ER (desvenlafaxine fumarate) to Pristiq (desvenlafaxine succinate) are the studies used to support dosing and claims.

A Randomized, Open Label, Three Treatment, Three Period, Six Sequence, Single Dose, Crossover, Bioequivalence Study Comparing SUN Pharmaceutical Industries Limited Desvenlafaxine 100mg Extended Release Tablets When Administered Under Fasting and Fed Condition and Pristiq® (Desvenlafaxine) 100mg Extended Release Tablets of Wyeth Pharmaceuticals Inc. when Administered Under Fasting Condition, in 36 Healthy Human Adult Subjects.

A Randomized, Open Label, Two Treatment, Two Period, Two Sequence, Single Dose, Crossover, Bioequivalence Study of Desvenlafaxine 50mg Extended Release Tablets of SUN Pharmaceutical Industries Limited, India and Pristiq® (Desvenlafaxine) 50mg Extended Release Tablets of Wyeth Pharmaceuticals Inc. in 50 Healthy Human Adult Subjects Under Fasting Conditions.

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

Desvenlafaxine Fumarate ER Tablets, 100 mg were bioequivalent to Pristiq® ER Tablets, 100 mg as shown in a study after administration of single dose of 100 mg Desvenlafaxine fumarate ER or Pristiq ER tablets under fasting conditions.

The sponsor conducted a randomized, open label, three treatment, three period, six sequence, single dose, crossover, bioequivalence study comparing Desvenlafaxine Fumarate100mg Extended Release Tablets (SUN) and Pristiq® (Desvenlafaxine succinate) 100mg Extended Release Tablets when administered under fasting condition in healthy human subjects to assess the bioequivalence between the two products under fasting conditions and determine the effect of food. The treatment arms of the study are as follows:
Treatment A: Single oral dose of Desvenlafaxine 100mg Extended Release Tablet administered under fasting condition.
Treatment B: Single oral dose of Desvenlafaxine 100mg Extended Release Tablet was administered under fed condition (30 minutes after administration of high-calorie high fat breakfast.
Treatment C: Single oral dose of Pristiq® (Desvenlafaxine) 100mg Extended Release Tablet was administered under fasting condition

The mean plasma concentration-time profiles after administration of 100 mg Desvenlafaxine fumarate or 100 mg Pristiq under fasting conditions are provided in Figure 4.

Figure 4: Mean Plasma Desvenlafaxine Concentration Time Profile after Administration of 100 mg Desvenlafaxine fumarate ER and Pristiq ER

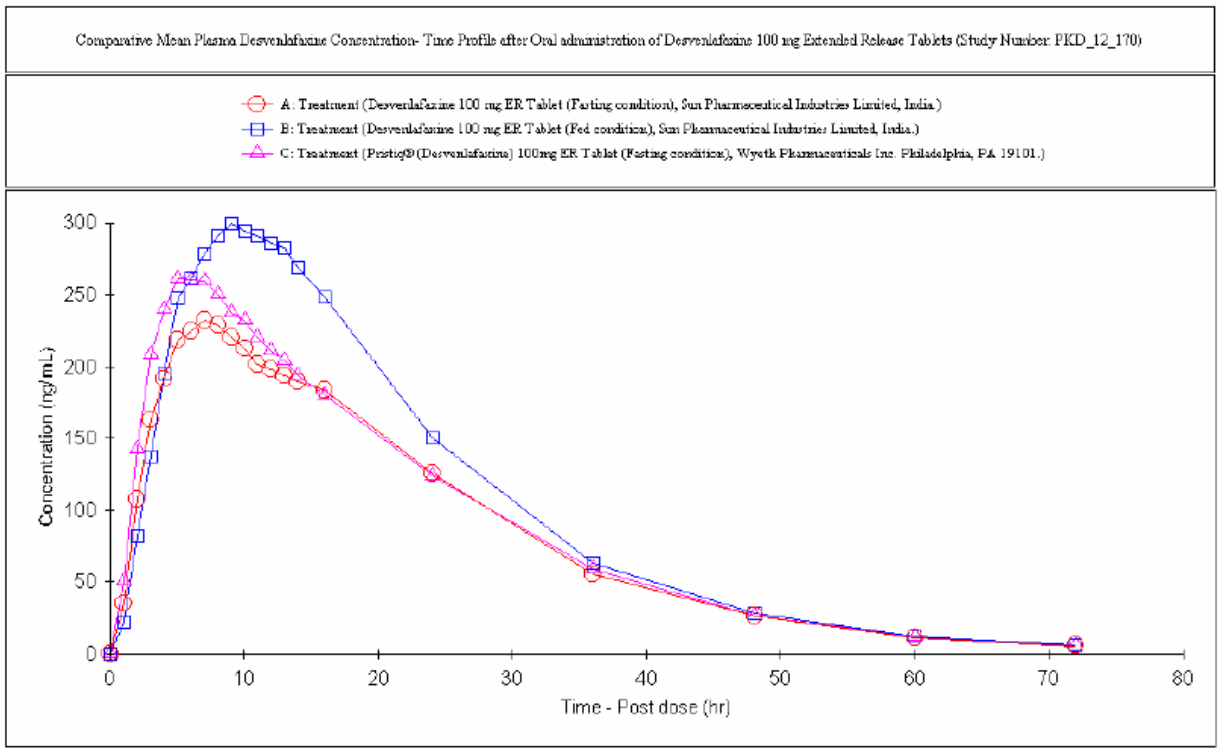



Table 6 contains the statistical analysis for Desvenlafaxine after administration of Desvenlafaxine fumarate ER and Pristiq ER under fasting conditions.

Table 6: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Treatments A or B to Healthy Subjects under Fasting Conditions (N=33)

| Parameter | Geometric Mean | | Ratio of Mean (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Treatment A (n=33) | Treatment C (n=33) | A/C | |
| Cmax (ng/mL) | 243.02 | 272.23 | 89.27 | 83.66 – 95.25 |
| AUCt (ng*hr/mL) | 5353.99 | 5994.04 | 89.32 | 80.96 – 98.55 |
| AUC∞ (ng*hr/mL) | 5433.11 | 6077.98 | 89.39 | 80.98 – 98.67 |
| Tmax [hr]* | 7.00 (3 – 16) | 6.00 (3 – 12) | | |
| T ½ [hr]# | 10.04 (1.32) | 10.13 (1.54) | | |

*Median (range); Mean# (± SD)
Trt A: Desvenlafaxine fumarate ER 100 mg under fasting conditions
Trt C: Pristiq ER 100 mg under fasting conditions

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 100 mg is bioequivalent to Pristiq ER under fasting conditions.

*2.2.3 Is Desvenlafaxine fumarate (SUN) 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 Tablets, 50 mg after administration of single doses of 50 mg desvenlafaxine fumarate ER tablets under fasting conditions.

The sponsor assessed the bioequivalence of Desvenlafaxine after administration of desvenlafaxine fumarate ER (SUN) and Pristiq ER 50 mg under fasting conditions. The study was a randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Desvenlafaxine 50mg Extended Release Tablets (SUN) and Pristiq® (Desvenlafaxine succinate) 50mg Extended Release tablets in healthy human adult subjects under fasting conditions.

The mean plasma concentration-time profiles after administration of Desvenlafaxine fumarate 50 mg or Pristiq 50 mg under fasting conditions are provided in Figure 5.

Figure 5: Mean Plasma Desvenlafaxine Concentration-time Profile

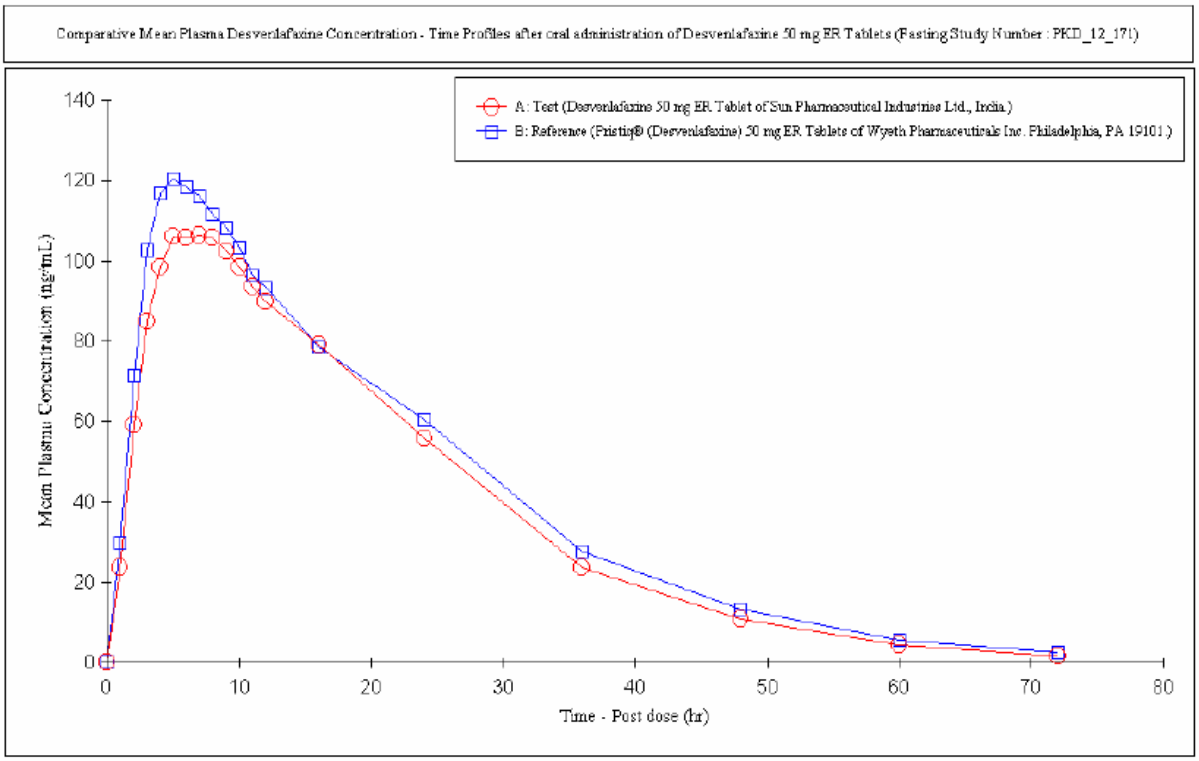


Table 7: Summary of Statistical Analysis Desvenlafaxine (N=47)

| Parameter | Geometric Mean | | Ratio of Mean (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Treatment A | Treatment B | A/B | |
| Cmax (ng/mL) | 114.05 | 124.17 | 91.86 | 87.71 – 96.20 |
| AUCt (ng*hr/mL) | 2507.46 | 2777.99 | 90.26 | 81.62 – 99.82 |
| AUC∞ (ng*hr/mL) | 2551.09 | 2829.92 | 90.15 | 81.58 – 99.61 |
| Tmax [hr][*] | 6.0 (3.0 – 16.0) | 5.0 (3.0 – 12.0) | | |
| T ½ [hr][#] | 9.6 (1.7) | 9.9 (2.0) | | |

[*]Median (range); Mean[#] (± SD)
Trt A: Desvenlafaxine fumarate ER 50 mg under fasting conditions
Trt B: Pristiq ER 50mg under fasting conditions

The 90% CIs of the ratios of Cmax, AUC (0-t), and AUC(0-∞) between test (Trt A) and reference (Trt B) are within the regulatory criteria (80% to 125%) for bioequivalence; therefore, Desvenlafaxine fumarate ER 50 mg is bioequivalent to Pristiq ER 50 mg under fasting conditions. There was no meaningful difference in Tmax and T ½ after administration of Desvenlafaxine ER 50 mg (SUN) and Pristiq ER 50 mg under fasting conditions.

*2.2.4 Is the exposure to Desvenlafaxine fumarate significantly different after administration of Desvenlafaxine fumarate 100 mg with or without food?*

The extent of exposure (AUC) was significantly higher (29%) when Desvenlafaxine fumarate ER (SUN) is administered with food compared to when administered without food. The peak concentration (Cmax) was significantly higher (37% higher) when Desvenlafaxine fumarate ER tablet is administered with food than when administered on an empty stomach. Food did increase the time to peak concentration (Tmax) by about 2.5 hours. The increase in exposure is not expected to result in significantly different adverse event profile from the reference product and therefore is not expected to be clinically relevant.

The mean plasma concentration time profile after administration of Desvenlafaxine fumarate ER 100 mg with or without food in presented in Figure 4 under Section 2.2.2.

Table 8 contains the statistical comparison of the pharmacokinetics of desvenlafaxine after administration of Desvenlafaxine fumarate ER 100 mg tablets with or without food.

Table 8: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Treatments A or B to Healthy Subjects under Fasting Conditions (N=33)

| Parameter | Geometric Mean | | Ratio of Mean (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Treatment A (n=33) | Treatment B (n=33) | B/A | |
| Cmax (ng/mL) | 243.02 | 332.93 | 136.99 | 127.65 – 146.11 |
| AUCt (ng*hr/mL) | 5353.99 | 6955.14 | 129.32 | 115.90 – 144.29 |
| AUC∞ (ng*hr/mL) | 5433.11 | 7039.71 | 129.57 | 115.62 – 143.89 |
| Tmax [hr][*] | 7.00 (3 – 16) | 9.50 (4 – 16) | | |
| T ½ [hr][#] | 10.04 (1.32) | 9.98 (1.26) | | |

[*]Median (range); Mean[#] (± SD)
Trt A: Desvenlafaxine fumarate ER 100 mg under fasting conditions
Trt B: Desvenlafaxine fumarate ER 100 mg under fed conditions

The 90% CIs of the ratio of Cmax and AUC between treatment B and treatment A were outside the confidence limits for bioequivalence. Therefore, a significant difference was observed when Desvenlafaxine fumarate ER was administered with food compared to when it was administered without food.

*2.2.5. How does the exposure to desvenlafaxine after administration of Desvenlafaxine fumarate ER with food compare to exposure after administration of Pristiq under fasting conditions?*

Statistically significant difference was found between treatments for Cmax and AUC after administration of Desvenlafaxine fumarate ER after administration with food compared to after administration of Pristiq without food. Desvenlafaxine 100 mg ER tablet (test formulation) when given with a high-calorie, high-fat breakfast, there was an increase in absorption (AUC (0-t) and AUC(0-inf) values that are about 17% higher than when Pristiq (reference) is administered in a fasting state. Cmax was about 22% higher and Tmax occurs 3.50 hours later. The difference in exposures observed is not expected to result in significant difference adverse event profile.

Table 9 contains the statistical comparison of the pharmacokinetics of desvenlafaxine after administration of Desvenlafaxine fumarate ER 100 mg tablets with food and Pristiq ER without food.

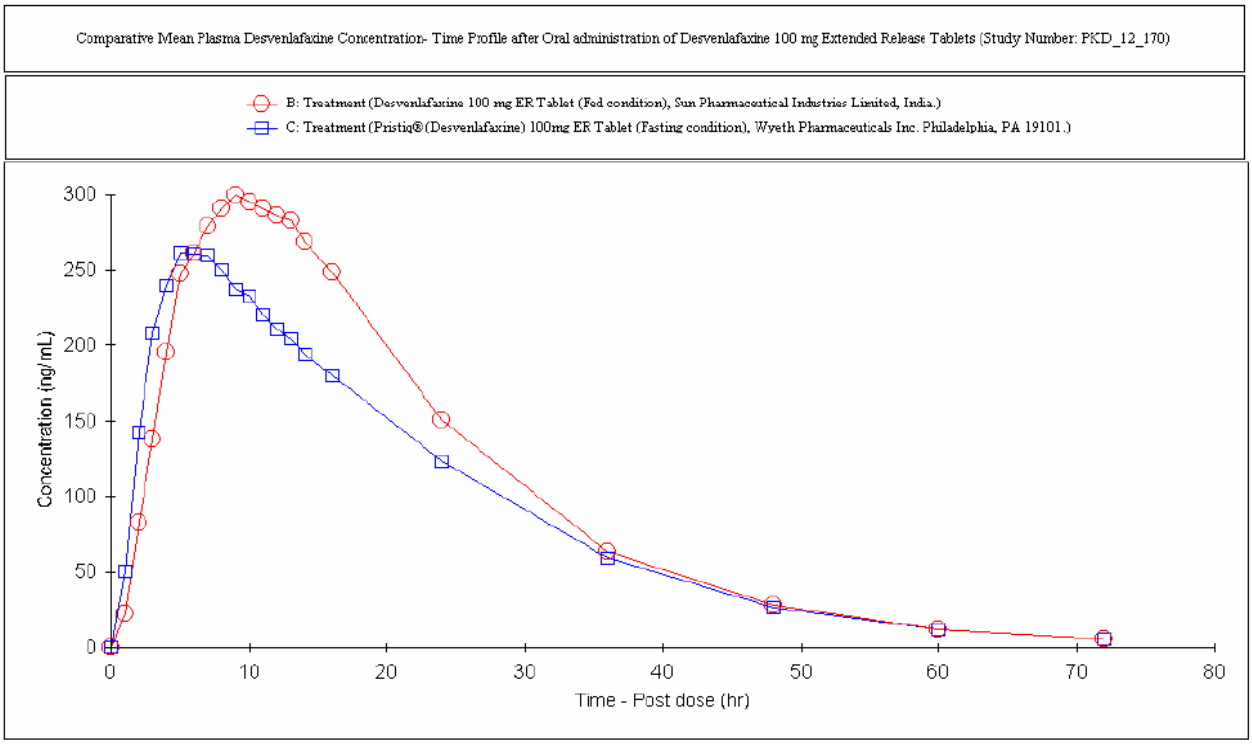
Table 9: Summary of Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after Administration Desvenlafaxine fumarate ER with Food and Pristiq ER 100 mg without Food

| Parameter | Geometric Mean | | Ratio of Mean (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Treatment B (n=33) | Treatment C (n=33) | B/C | |
| Cmax (ng/mL) | 332.63 | 271.70 | 122.43 | 115.03 – 130.29 |
| AUCt (ng*hr/mL) | 6963.70 | 5961.82 | 116.80 | 107.75 – 126.62 |
| AUC∞ (ng*hr/mL) | 7047.88 | 6045.28 | 116.58 | 107.51 – 126.43 |
| Tmax [hr]* | 9.5 (4.0 – 16.0) | 6.0 (3.0 -12.0) | | |
| T ½ [hr]# | 9.98 (1.25) | 10.13 (1.54) | | |

*Median (range); Mean# (± SD)
Trt B: Desvenlafaxine fumarate ER 100 mg with food
Trt C: Pristiq ER 100 mg under fasting conditions

Figure 6: is the mean plasma concentration-time profile of Desvenlafaxine after Desvenlafaxine ER 100 mg tablet administered under fed conditions and Pristiq ER 100 mg administered under fasting conditions.

Figure 6: Mean Plasma Concentration Time Profile of Desvenlafaxine



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

After administration of Desvenlafaxine fumarate 50 mg ER tablet, the mean (SD) elimination half-life (T ½) was 9.6 (1.7) hours which is similar to that observed after administration of Pristiq, 9.9 (2) hours. The median (range) time to peak concentration (Tmax) was 6 (3.0 – 16) 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).

*2.2.7 What is the composition of Desvenlafaxine fumarate ER formulations used in the bioequivalence studies?*

Table 10 contains the qualitative and quantitative composition of Desvenlafaxine fumarate ER 50 mg and 100 mg.

Table 10: Composition of Desvenlafaxine fumarate ER Tablets

| Ingredient | Function | mg/unit (50 mg) | mg/unit (100 mg) |
|---|---|---|---|
| Desvenlafaxine Fumarate | Active | 72.035 | 144.070 |
| Hypromellose (b) (4) USP | | | |
| Microcrystalline Cellulose (b) (4) NF | | | |
| Magnesium Stearate, NF | | | |
| Ferric Oxide Red[2] | | | |
| Talc, USP | | | |
| Magnesium Stearate, NF | | | |
| Colloidal silicon Dioxide, NF | | | |
| Film-Coati | | | |
| Hypromellose (b) (4) USP | | | |
| Titanium Dioxide, USP | | | |
| PEG (b) (4) NF | | | |
| Talc, USP | | | |
| Ferric Oxide Red[2], NF | | | |
| Ferric Oxide Yellow[2], NF | | | |
| **Total Weight of Coated Tablets:** | | 463.500 | 463.500 |

*2.3 Analytical Methods*

*2.3.1 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.

*2.3.2. 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 analyte is 1.54 to 516.59 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

| | | |
|---|---|---|
| Analyte | Des-Methyl Venlafaxine | |
| Internal Standard (IS) | (b) (4) | |
| Limit of quantitation | LLOQ : 1.54ng/mL, ULOQ : 516.59ng/mL<br>LLOQ : 1.58ng/mL, ULOQ : 514.16ng/mL (*) | |
| Relative recovery of analyte (%) | QC Low A: 68.3%<br>QC Low B: 66.2%<br>QC Med A: 72.5%<br>QC Med B: 73.5%<br>QC High : 82.3% | |
| Relative recovery of IS (%) | 70.7% | |
| Absolute recovery of analyte (%) | QC Low A: 83.3%<br>QC Low B: 80.1%<br>QC Med A: 85.1%<br>QC Med B: 84.8%<br>QC High : 96.0% | |
| Absolute recovery of IS (%) | 84.5% | |
| Standard curve concentrations (ng/mL) | 1.54, 3.08, 34.77, 84.44, 116.73, 223.52, 317.90, 397.38, 516.59<br>1.58, 3.16, 34.61, 84.05, 116.18, 222.48, 316.41, 395.51, 514.16 (*) | |
| QC Concentrations (ng/mL) | Low QC A: 4.58<br>Low QC B: 13.75<br>Medium QC A : 149.41<br>Medium QC B : 249.01<br>High QC : 428.30 | Low QC A: 4.73 (*)<br>Low QC B: 14.18 (*)<br>Medium QC A : 150.87 (*)<br>Medium QC B : 251.46 (*)<br>High QC : 427.48 (*) |
| QC Intraday precision range (%) | 0.8 % to 10.3% | |
| QC Intraday accuracy range (%) | 86.9% to 108.2% | |
| QC Inter day precision range (%) | 0.8 % to 10.3% | |
| QC Inter day accuracy range (%) | 86.9% to 110.3% | |
| Bench-top stability (hrs) | 10 hours at room temperature (in Plasma) | |
| | 3 hours at room temperature (in Blood) | |
| Stock solution stability (days) | 11 days @ 2-8°C for Analyte & 16 days @ 2-8°C for IS | |
| Post-Processed stability (hrs) | 70 hours @ 10±2°C | |
| Post Extraction Bench Top Stability | 15 hours at room temperature | |
| Freeze-thaw stability (cycles) | 04 cycles at -20±5°C, -35±5°C & -65±10°C | |
| Long term storage stability (Days) | 89 days at -20±5°C & -65±10°C, 91 days at -35±5°C | |
| Dilution Integrity | 1.5-3 times ULOQ concentration (1045.86ng/mL) diluted 5 folds. | |
| | % Accuracy: 1/5th: 101.5 | |
| | % Precision : 1/5th: 1.3 | |
| Selectivity | No interference observed in blank plasma samples | |

(*): The calibration standards and Quality control samples were prepared for Long term storage stability experiment.

# 3. Appendix

## *3.1. Individual Studies*

**Biopharmaceutics**

| | | |
|---|---|---|
| **Report # PKD-12-170** | **Study Period**: 5/26/2012 – 12/18/2012 | EDR Link:\\cdsesub1\EVSPROD\NDA205583\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep |
| **Title** | A Randomized, Open Label, Three Treatment, Three Period, Six Sequence, Single Dose, Crossover, Bioequivalence Study Comparing Sun Pharmaceutical Industries Limited India's Desvenlafaxine 100mg Extended Release Tablets When Administered Under Fasting And Fed Condition And Pristiq® (Desvenlafaxine) 100mg Extended Release Tablets Of Wyeth Pharmaceuticals Inc. Philadelphia, Pa 19101, When Administered Under Fasting Condition, In 36 Healthy Human Adult Subjects. | |

| | |
|---|---|
| **Objectives** | To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Desvenlafaxine 100mg Extended Release Tablets of Sun Pharmaceutical Industries Limited, India and Pristiq® (Desvenlafaxine) 100mg Extended Release Tablets of Wyeth Pharmaceuticals Inc., Philadelphia, PA 19101, in 36 healthy human adult subjects, under fasting conditions and to evaluate effect of food on pharmacokinetic parameters of Desvenlafaxine 100mg Extended Release Tablets of Sun Pharmaceutical Industries Limited, India, when administered under fasting and fed condition. |

**Study Design**

| | |
|---|---|
| ☑ Bioequivalence | ☐ Bioavailability |

Single-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy Vonuteers
Six –sequence, three treatment

| | |
|---|---|
| **Screening:** ≤ 21 days | **Washout:** ≥ 7 days, outpatient |
| **Period 1/2** | 84 hours, Inpatient stay ☑Y ☐ N: |

**Treatments:** (Active Ingredient: Desvenlafaxine)

| | **Test** | **Reference** |
|---|---|---|
| Dosage Form | Tablet | Tablet |
| Dosage Strength | 100 mg | 100 mg |
| Batch #. | JKL1223Alo | E70999 |
| Administration | Oral | Oral |
| | | |

**Treatment**

**Treatment A:** Single oral dose of Desvenlafaxine 100mg Extended Release Tablet was administered with 240 mL (± 2 mL) of water at ambient temperature under fasting condition.
**Treatment B:** Single oral dose of Desvenlafaxine 100mg Extended Release Tablet was administered with 240 mL (± 2 mL) of water at ambient temperature under fed condition (30 minutes after administration of high-calorie highfat breakfast.
**Treatment C:** Single oral dose of Pristiq® (Desvenlafaxine) 100mg Extended Release Tablet was administered with 240 mL (± 2 mL) of water at ambient temperature under fasting condition

| Composition of Non Standard FDA Meal used in food effect Bioequivalence study | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Serial Number | Ingredients | | Amount (g) | | Energy (Kcal) | Protein (Kcal) | Fat (Kcal) | Carbohydrate (Kcal) |
| | | | Raw Weight (g) | Cooked Weight (g) | | | | |
| **SANDWICH** | | | | | | | | |
| 1 | Omelet | 2 Eggs | 120 | 295 | 208 | 64.00 | 144.00 | - |
| 2 | | Onion | 20 | | 11.52 | 1.44 | - | 10.08 |
| 3 | | Green Chilies | 5 | | 0.6 | 0.60 | - | - |
| 4 | Boiled Potato (Hash brown) | | 120 | | 116 | 8.00 | - | 108.00 |
| 5 | 2 Slices of bread (Toasted) | | 48 | | 116.4 | 14.00 | 9.00 | 93.40 |
| 6 | Goat meat | | 24 | | 24.48 | 20.16 | 4.32 | - |
| 7 | Butter | | 30 | | 216 | - | 216.00 | - |
| 8 | Cheese | | 30 | | 104.25 | 28.92 | 67.77 | 7.56 |
| **MILK** | | | | | | | | |
| 1 | Milk (cow's) | | 240 mL | 240 | 166 | 32.00 | 90.00 | 44.00 |
| 2 | Sugar | | 5 | | 20 | - | - | 20.00 |
| **TOTAL ( K calories)** | | | | | **983.25** | **169.12** | **531.09** | **283.04** |
| **Percent of Total Kcal** | | | | | **100.00** | **17.20** | **54.01** | **28.79** |

**Sampling Times (PK, plasma)**

- Test: 0,1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 24, 36, 48, 60, 72 hours post dose
- Reference: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 24, 36, 48, 60, 72 hours post dose

**Analytical Method:**

.

Validated LC/MS/MS.

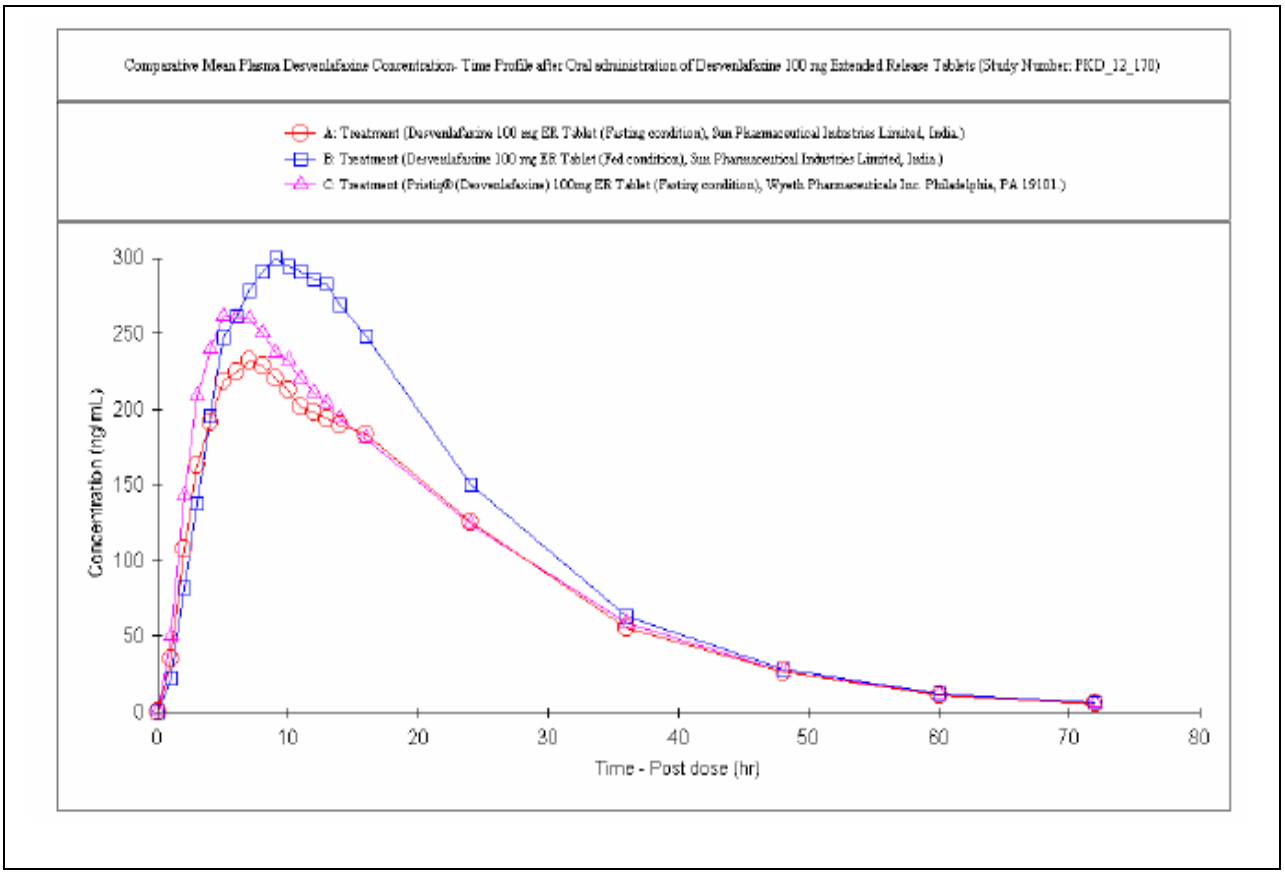
**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 40/36/4 |
| Age [ Mean ± SD (range)] | 33.5 ± 6.98 (20 -44) years |
| Male/Female | 36/0 |
| Race (Caucasian/Black/Asian/other) | 0/0/36/0 |

**Results**

Mean plasma desvenlafaxine concentration time profile after administration of 100 mg Desvenlafaxine fumarate ER and Pristiq ER


Comparative Mean Plasma Desvenlafaxine Concentration- Time Profile after Oral administration of Desvenlafaxine 100 mg Extended Release Tablets (Study Number: PKD_12_170)
A: Treatment (Desvenlafaxine 100 mg ER Tablet (Fasting condition), Sun Pharmaceutical Industries Limited, India.)
B: Treatment (Desvenlafaxine 100 mg ER Tablet (Fed condition), Sun Pharmaceutical Industries Limited, India.)
C: Treatment (Pristiq®(Desvenlafaxine) 100mg ER Tablet (Fasting condition), Wyeth Pharmaceuticals Inc. Philadelphia, PA 19101.)
Concentration (ng/mL)
300
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
Time - Post dose (hr)

| TABLE 14.2 –1A | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| SUMMARY OF RESULTS | | | | | | | | |
| DESVENLAFAXINE (N =33) | | | | | | | | |
| Pharmacokinetic Parameters | | | | | | | | |
| Treatment 'A' vs. 'C' | | | | | | | | |
| Parameters | Desvenlafaxine 100 mg ER Tablets under fasting condition Treatment A | | | | Pristiq® (Desvenlafaxine) 100 mg ER Tablets under fasting condition Treatment C | | | |
| | Mean ± | | SD | CV% | Mean | ± | SD | CV% |
| $AUC_{0-t}$ (ng.h/mL) | 6031.6574 ± | | 2667.00898 | 44.2 | 6400.6685 | ± | 2166.18421 | 33.8 |
| $AUC_{0-inf}$ (ng.h/mL) | 6122.0650 ± | | 2717.31078 | 44.4 | 6496.2111 | ± | 2221.45467 | 34.2 |
| $C_{max}$ (ng/mL) | 254.544 ± | | 83.4623 | 32.8 | 278.254 | ± | 60.4712 | 21.7 |
| $T_{max}$ (h) | 8.000 | ± | 3.4641 | 43.3 | 6.303 | ± | 1.9119 | 30.3 |
| $T_{max}$* (h) | 7.00 (3.00 - 16.00 ) | - | - | - | 6.00 (3.00 - 12.00 ) | - - | | - |
| $K_{el}$ ($h^{-1}$) 0. | 07028 | ± | 0.010303 | 14.7 | 0.07002 | ± | 0.011007 | 15.7 |
| $T_{1/2}$ (h) | 10.0487 | ± | 1.32433 | 13.2 | 10.1303 | ± | 1.54942 | 15.3 |
| % $AUC_{0-t}$ / $AUC_{0-inf}$ | 98.554 ± | | 0.6528 | 0.7 | 98.636 | ± | 0.6697 | 0.7 |
| % AUC Extrapolation | 1.446 ± | | 0.6528 | 45.2 | 1.364 | ± | 0.6697 | 49.1 |

*Median values (range) are presented.

Source: Appendix 16.2.6.1

Summary of Pharmacokinetic Parameters with Statistical Evaluation

| SUMMARY OF STATISTICAL ANALYSIS DESVENLAFAXINE (N =33) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ln- Transformed Data | | | | | | | | |
| PK Variables | Least Square Means | | Geometric Means[3] | | Ratio of Least-Square Means[1] % | 90% Geometric C.I.[2] | Intra-Subject CV% | p-value[4] |
| | Treatment A | Treatment C | Treatment A | Treatment C | | | | |
| $AUC_{0-t}$ | 8.59 8. | 70 | 5353.99 | 5994.04 | 89.32 | 80.96 to 98.55 | 23.84 | 0.0607 |
| $AUC_{0-inf}$ | 8.60 8. | 71 | 5433.11 | 6077.98 | 89.39 | 80.98 to 98.67 | 23.95 | 0.0635 |
| $C_{max}$ | 5.49 5. | 61 | 243.02 | 272.23 | 89.27 | 83.66 to 95.25 | 15.60 | 0.0058 |

Source: Appendix 16.1.9.1

[1] Calculated using least square means according to the formula: $e^{(LSM\ Treatment\ (A) - LSM\ Treatment\ (C))} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data;

[3] Least-square geometric means calculated from the analysis of the Ln-transformed data as $e^{(least\text{-}square\ mean)}$

[4] p-value is for product effect

| TABLE 14.2 –2A | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| SUMMARY OF RESULTS | | | | | | | | |
| DESVENLAFAXINE (N =33)# | | | | | | | | |
| Pharmacokinetic Parameters | | | | | | | | |
| Treatment 'B' vs. 'A' | | | | | | | | |
| Parameters | Desvenlafaxine 100 mg ER Tablets under fed condition Treatment B | | | | Desvenlafaxine 100 mg ER Tablets under fasting condition Treatment A | | | |
| | Mean ± | | SD | CV% | Mean | ± | SD | CV% |
| $AUC_{0-t}$ (ng.h/mL) | 7393.0853 ± | | 2001.64299 | 27.1 | 6031.6574 | ± | 2667.00898 | 44.2 |
| $AUC_{0-inf}$ (ng.h/mL) | 7487.2589 ± | | 2056.04029 | 27.5 | 6122.0650 | ± | 2717.31078 | 44.4 |
| $C_{max}$ (ng/mL) | 342.657 ± | | 80.9323 | 23.6 | 254.544 | ± | 83.4623 | 32.8 |
| $T_{max}$ (h) | 9.625 | ± | 3.2404 | 33.7 | 8.000 | ± | 3.4641 | 43.3 |
| $T_{max}$* (h) | 9.50 (4.00 - 16.00 ) | | - | - | 7.00 (3.00 - 16.00 ) | | - | - |
| $K_{el}$ ($h^{-1}$) 0. | 07055 | ± | 0.009143 | 13.0 | 0.07028 | ± | 0.010303 | 14.7 |
| $T_{1/2}$ (h) | 9.9822 | ± | 1.25631 | 12.6 | 10.0487 | ± | 1.32433 | 13.2 |
| % $AUC_{0-t}$ / $AUC_{0-inf}$ | 98.823 ± | | 0.5623 | 0.6 | 98.554 | ± | 0.6528 | 0.7 |
| % AUC Extrapolation | 1.178 ± | | 0.5623 | 47.8 | 1.446 | ± | 0.6528 | 45.2 |

*Median values (range) are presented. # N= 32 for treatment B

Source: Appendix 16.2.6.1

| Parameter | Geometric Mean | | Ratio of Mean (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Treatment A (n=33) | Treatment B (n=33) | B/A | |
| Cmax (ng/mL) | 243.02 | 332.93 | 136.99 | 127.65 – 146.11 |
| AUCt (ng*hr/mL) | 5353.99 | 6955.14 | 129.32 | 115.90 – 144.29 |
| AUC∞ (ng*hr/mL) | 5433.11 | 7039.71 | 129.57 | 115.62 – 143.89 |
| Tmax [hr]* | 7.00 (3 – 16) | 9.50 (4 – 16) | | |
| T ½ [hr]# | 10.04 (1.32) | 9.98 (1.26) | | |

*Median (range); Mean# (± SD)

Trt A: Desvenlafaxine fumarate ER 100 mg under fasting conditions

Trt B: Desvenlafaxine fumarate ER 100 mg under fed conditions

| SUMMARY OF RESULTS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| DESVENLAFAXINE (N = 33)# | | | | | | | | |
| Pharmacokinetic Parameters | | | | | | | | |
| Parameters | Desvenlafaxine 100 mg ER Tablets under fed condition Treatment B | | | | Pristiq® (Desvenlafaxine) 100 mg ER Tablets under fasting condition Treatment C | | | |
| | Mean | ± | SD | CV % | Mean | ± | SD | CV% |
| $AUC_{0-t}$ (ng.h/mL) | 7393.0853 | ± | 2001.64299 | 27.1 | 6400.6685 | ± | 2166.18421 | 33.8 |
| $AUC_{0-inf}$ (ng.h/mL) | 7487.2589 | ± | 2056.04029 | 27.5 | 6496.2111 | ± | 2221.45467 | 34.2 |
| $C_{max}$ (ng/mL) | 342.657 | ± | 80.9323 | 23.6 | 278.254 | ± | 60.4712 | 21.7 |
| $T_{max}$ (h) | 9.625 | ± | 3.2404 | 33.7 | 6.303 | ± | 1.9119 | 30.3 |
| $T_{max}$* (h) | 9.50 (4.00 - 16.00 ) | - | - | - | 6.00 (3.00 - 12.00 ) | - | - | - |
| $K_{el}$ ($h^{-1}$) | 0.07055 | ± | 0.009143 | 13.0 | 0.07002 | ± | 0.011007 | 15.7 |
| $T_{1/2}$ (h) | 9.9822 | ± | 1.25631 | 12.6 | 10.1303 | ± | 1.54942 | 15.3 |
| % $AUC_{0-t}$ / $AUC_{0-inf}$ | 98.823 | ± | 0.5623 | 0.6 | 98.636 | ± | 0.6697 | 0.7 |
| %AUC Extrapolation | 1.178 | ± | 0.5623 | 47.8 | 1.364 | ± | 0.6697 | 49.1 |

*Median values (range) are presented. # N= 32 for treatment B  **Source: Appendix 3A**

| SUMMARY OF STATISTICAL TOTAL DESVENLAFAXINE (N = 33)# | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ln- Transformed Data | | | | | | | | |
| PK Variables | Least Square Means | | Geometric Means[3] | | Ratio of Least-Square Means[1] % | 90% Geometric C.I.[2] | Intra-Subject CV % | P-value [4] |
| | Treatment B | Treatment C | Treatment B | Treatment C | | | | |
| $AUC_{0-t}$ | 8.85 | 8.69 | 6963.70 | 5961.82 | 116.80 | 107.75 to 126.62 | 19.16 | 0.0028 |
| $AUC_{0-inf}$ | 8.86 | 8.71 | 7047.88 | 6045.28 | 116.58 | 107.51 to 126.43 | 19.24 | 0.0032 |
| $C_{max}$ | 5.81 | 5.60 | 332.63 | 271.70 | 122.43 | 115.03 to 130.29 | 14.73 | < 0.0001 |

**Source: Appendix 1**

[1] Calculated using least square means according to the formula: $e^{(\text{LSM Treatment (B)} - \text{LSM Treatment (C)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data;
[3] Least-square geometric means calculated from the analysis of the Ln-transformed data as $e^{(\text{least-square mean})}$
[4] p-value is for product effect
# N= 32 for treatment B

Mean plasma desvenlafaxine concentration time profile after administration of 100 mg Desvenlafaxine fumarate ER and Pristiq ER

**Site Inspected**

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

**Safety**

Out of 9 adverse events, 7 (77.8% of 9) adverse events were experienced by 3 (8.6% of 35) subjects when received treatment A and all these 3 subjects were dropped due to adverse event. 1 (11.1% of 9) adverse event was experienced by 1 (2.9% of 34) subject when received treatment C and dropped from the study due to adverse event. Remaining 1 (11.1% of 9) adverse event which was considered to have emerged from all three treatments occurred in 1 (3.1% of 32)

| |
|---|
| subject. No death occurred during the study. One subject (subject number 34) experienced serious adverse event in period II of the study. Most common adverse event reported was diarrhea which occurred on 4 occasions, 3 times with the treatment A and 1 time with treatment C. |
| **Conclusion** |
| The 90% confidence intervals of the relative mean AUCt, AUCinf and Cmax of the test to reference products under fasting condition are within the 80-125% bioequivalence range. Hence, Desvenlafaxine fumarate 50 mg (Teva) is bioequivalent to Pristiq under fasting conditions. Food increases the peak systemic exposure (Cmax) and extent of exposure (AUC) by ~36% and 29%, respectively compared to the fasting state. |
| **Comments** |
| The median Tmax is about 2.5 hours longer after administration Desvenlafaxine fumarate ER under fed conditions compared to Desvenlafaxine ER under fasting conditions. Food has a significant effect on the absorption of desvenlafaxine after administration of desvenlafaxine fumarate under fed conditions. When Desvenlafaxine fumarate ER under fed conditions is compared to Pristiq under fasting conditions, the magnitude of the effect of food is not as large as that seen when compared to Desvenlafaxine fumarate ER under fasting. Therefore, the effect of food may not be clinically relevant. |

**Biopharmaceutics-**

| **Report # PKD-12-171** | **Study Period**: 8/3/12 to 12/12/12 | EDR Link: \\cdsesub1\EVSPROD\nda205583\0000\m5 |
|---|---|---|
| **Title** | A Randomized, Open Label, Two Treatment, Two Period, Two Sequence, Single Dose, Crossover, Bioequivalence Study of Desvenlafaxine 50mg Extended Release Tablets of Sun Pharmaceutical Industries Limited, India and Pristiq® (Desvenlafaxine) 50mg Extended Release Tablets of Wyeth Pharmaceuticals Inc. Philadelphia, Pa 19101 In 50 Healthy Human Adult Subjects Under Fasting Conditions. | |
| **Objectives** | To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Desvenlafaxine 50mg Extended Release Tablets of Sun Pharmaceutical Industries Limited, India and Pristiq® (Desvenlafaxine) 50 mg Extended Release Tablets of Wyeth Pharmaceuticals Inc., Philadelphia, PA 19101, in 50 healthy human adult subjects, under fasting conditions. | |
| **Study Design** | | |
| ☑ Bioequivalence | Bioavailability | |
| Single-Dose Randomized Open-Label Cross-Over Single-Center, 2-Period, 2-Treatment, 2-Sequence Healthy Vonuteers | | |
| **Screening:** ≤ 21 days | **Washout:** ≥ 7 days, outpatient | |
| **Period 1/2** | 84 hours , Inpatient stay ☑Y ☐ N: | |
| **Treatments:** (Active Ingredient: Desvenlafaxine) | | |

| | Test | Reference |
|---|---|---|
| Dosage Form | ER Tablet | ER Tablet |
| Dosage Strength | 50 mg | 50 mg |
| Batch #. | JKL1641A | E89895 |
| Administration | Oral | Oral |
| | | |

**Test A:** Single oral dose of Desvenlafaxine 50 mg Extended Release (ER) Tablet was administered with 240 mL (± 2 mL) of water at ambient temperature.
**Reference B:** Single oral dose of Pristiq® (Desvenlafaxine) 50 mg Extended Release Tablet was administered with 240 mL (± 2 mL) of water at ambient temperature.

**Sampling Times (PK, plasma)**

- Test: pre-dose (0), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 36, 48, 60, 72 hours post dose
- Reference: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 36, 48, 60, 72 hours post dose

**Analytical Method:** The performance of the analytical method is acceptable. Yes ☑ No ☐
LC/MS/MS.

| | | |
|---|---|---|
| Analyte | Des-Methyl Venlafaxine | |
| Internal Standard (IS) | (b) (4) | |
| Limit of quantitation | LLOQ : 1.54ng/mL, ULOQ : 516.59ng/mL<br>LLOQ : 1.58ng/mL, ULOQ : 514.16ng/mL (*) | |
| Relative recovery of analyte (%) | QC Low A: 68.3%<br>QC Low B: 66.2%<br>QC Med A: 72.5%<br>QC Med B: 73.5%<br>QC High : 82.3% | |
| Relative recovery of IS (%) | 70.7% | |
| Absolute recovery of analyte (%) | QC Low A: 83.3%<br>QC Low B: 80.1%<br>QC Med A: 85.1%<br>QC Med B: 84.8%<br>QC High : 96.0% | |
| Absolute recovery of IS (%) | 84.5% | |
| Standard curve concentrations (ng/mL) | 1.54, 3.08, 34.77, 84.44, 116.73, 223.52, 317.90, 397.38, 516.59<br>1.58, 3.16, 34.61, 84.05, 116.18, 222.48, 316.41, 395.51, 514.16 (*) | |
| QC Concentrations (ng/mL) | Low QC A: 4.58<br>Low QC B: 13.75<br>Medium QC A : 149.41<br>Medium QC B : 249.01<br>High QC : 428.30 | Low QC A: 4.73 (*)<br>Low QC B: 14.18 (*)<br>Medium QC A : 150.87 (*)<br>Medium QC B : 251.46 (*)<br>High QC : 427.48 (*) |
| QC Intraday precision range (%) | 0.8 % to 10.3% | |
| QC Intraday accuracy range (%) | 86.9% to 108.2% | |
| QC Inter day precision range (%) | 0.8 % to 10.3% | |
| QC Inter day accuracy range (%) | 86.9% to 110.3% | |
| Bench-top stability (hrs) | 10 hours at room temperature (in Plasma) | |
| | 3 hours at room temperature (in Blood) | |
| Stock solution stability (days) | 11 days @ 2-8°C for Analyte & 16 days @ 2-8°C for IS | |
| Post-Processed stability (hrs) | 70 hours @ 10±2°C | |
| Post Extraction Bench Top Stability | 15 hours at room temperature | |
| Freeze-thaw stability (cycles) | 04 cycles at -20±5°C, -35±5°C & -65±10°C | |
| Long term storage stability (Days) | 89 days at -20±5°C & -65±10°C, 91 days at -35±5°C | |
| Dilution Integrity | 1.5-3 times ULOQ concentration (1045.86ng/mL) diluted 5 folds. | |
| | % Accuracy: 1/5th: 101.5 | |
| | % Precision : 1/5th: 1.3 | |
| Selectivity | No interference observed in blank plasma samples | |

(*): The calibration standards and Quality control samples were prepared for Long term storage stability experiment.

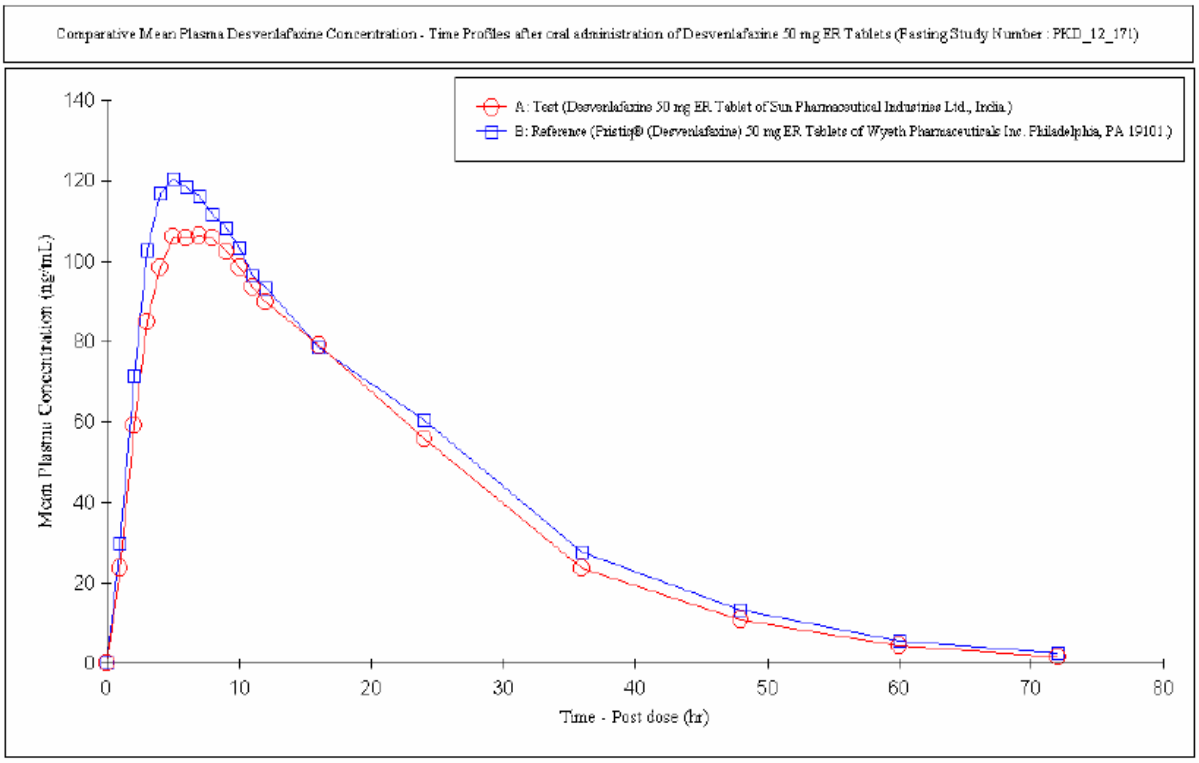
**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 50/47/3 |
| Age [ Mean ± SD (range)] | 32.5 ± 6.27 years ( 21 - 44) years |
| Male/Female | 50/0 |
| Race (Caucasian/Black/Asian/other) | 0/0/50/0 |

**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

| SUMMARY OF RESULTS<br>DESVENLAFAXINE (N = 47)<br>Pharmacokinetic Parameters | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Parameters | Desvenlafaxine 50 mg Extended Release Tablets Test (A) | | | | Pristiq® (Desvenlafaxine) 50 mg Extended Release Tablets Reference (B) | | | |
| | Mean | ± | SD | CV% | Mean | ± | SD | CV% |
| $AUC_{0-t}$ (ng.h/mL) | 2710.2588 | ± | 1006.92044 | 37.2 | 2970.4054 | ± | 1137.78783 | 38.3 |
| $AUC_{0-inf}$ (ng.h/mL) | 2754.5557 | ± | 1023.81951 | 37.2 | 3034.7351 | ± | 1220.71081 | 40.2 |
| $C_{max}$ (ng/mL) | 116.313 | ± | 22.1635 | 19.1 | 126.289 | ± | 23.7658 | 18.8 |
| $T_{max}$ (h) | 7.383 | ± | 3.5481 | 48.1 | 5.915 | ± | 2.0412 | 34.5 |
| $T_{max}$* (h) | 6.00 (3.00 - 16.00 ) | - | - | - | 5.00 (3.00 - 12.00) | - | - | - |
| $K_{el}$ ($h^{-1}$) | 0.07376 | ± | 0.010779 | 14.6 | 0.07228 | ± | 0.011857 | 16.4 |
| $T_{1/2}$ (h) | 9.6285 | ± | 1.66277 | 17.3 | 9.9058 | ± | 2.03666 | 20.6 |
| $\%AUC_{0-t}$ / $AUC_{0-inf}$ | 98.297 | ± | 0.9223 | 0.9 | 98.178 | ± | 1.5490 | 1.6 |
| % AUC Extrapolation | 1.703 | ± | 0.9223 | 54.2 | 1.822 | ± | 1.5490 | 85.0 |

*Median values (range) are presented.

**Source:** Appendix 16.2.6.1

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

| SUMMARY OF STATISTICAL ANALYSIS DESVENLAFAXINE (N = 47)<br>Ln- Transformed Data | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| PK Variables | Least Square Means | | Geometric Means[3] | | Ratio of Least-Square Means[1] % | 90% Geometric C.I.[2] | Intra-Subject CV% | p-value[4] |
| | Test | Reference | Test | Referenc | | | | |
| **$AUC_{0-t}$** | 7.83 | 7.93 | 2507.46 | 2777.99 | 90.26 | 81.62 to 99.82 | 29.67 | 0.0942 |
| **$AUC_{0-inf}$** | 7.84 | 7.95 | 2551.09 | 2829.92 | 90.15 | 81.58 to 99.61 | 29.42 | 0.0878 |
| **$C_{max}$** | 4.74 | 4.82 | 114.05 | 124.17 | 91.86 | 87.71 to 96.20 | 13.40 | 0.0035 |

**Source:** Appendix 16.1.9.1

[1] Calculated using least square means according to the formula: $e^{(\text{LSM Treatment (A)} - \text{LSM Treatment (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data;
[3] Least-square geometric means calculated from the analysis of the Ln-transformed data as $e^{(\text{least-square mean})}$
[4] p-value is for product effect

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

| |
|---|
| Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA<br>Out of 50 subjects, 3 subjects experienced 3 post dose adverse events. The sponsor stated that all 3 post dose adverse events were single treatment emergent adverse events. Out of 3 adverse events, 1 (33.3%) adverse event was experienced by 1 subject who received treatment A and was dropped from the study. Remaining 2 (66.7 %) adverse events were experienced by 2 subjects who received treatment B and both these subjects were dropped from the study. No subject experienced death or any serious adverse event during the study. The adverse event in the patient in Treatment A was vomiting. One subject in Treatment B experienced diarrhea and the other musculoskeletal pain. The sponsor reported that there was no significant difference between safety profiles of test and reference products. |
| **Conclusion** |
| The 90% confidence intervals calculated from the Ln-transformed data on the least square means ratios (test/reference) for AUC0-t, AUC0-inf and Cmax values were within the limits of 80.00% to 125.00%. Therefore, the Test (A) and Reference (B) formulations can be declared as bioequivalent when administered under fasting condition. |
| **Comments** |
| The reviewer agrees with the sponsor's conclusions that the 90% CI for the ratio of the mean of the test to reference product were within the accepted regulatory criteria for bioequivalence. Therefore the two products are bioequivalent. It must be noted that the 90% CI did not include 100 and was on the lower end of the confidence interval. The exposure to desvenlafaxine after administration of this Desvenlafaxine ER 50 mg tablet was about 10% lower than that observed after administration of Pristig ER 50 mg tablet. The median Tmax was about 1 hour longer after administration of this Desvenlafaxine ER 50 mg than the Tmax observed after administration of Pristiq ER 50 mg. These differences are not expected to be clinically relevant. |

*3.2. OSI Report (Refer to OSI report)*

---

**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
12/21/2013

HAO ZHU
12/22/2013

| BIOPHARMACEUTICS REVIEW<br>Office of New Drug Quality Assessment | | | |
|---|---|---|---|
| **Application No.:** | NDA 205583 | **Biopharmaceutics Reviewer:** Elsbeth Chikhale, PhD | |
| **Submission Date:** | March 28, 2013 | | |
| **Division:** | Division of Psychiatry Products | **Biopharmaceutics Team Leader:** Angelica Dorantes, PhD | |
| **Applicant:** | Sun Pharma Global FZE | **Acting Supervisor:** Richard Lostritto, PhD | |
| **Trade Name:** | TBD | **Date Assigned:** | April 8, 2013 |
| **Generic Name:** | Desvenlafaxine Extended Release Tablets | **Date of Review:** | December 13, 2013 |
| **Indication:** | Treatment of major depressive disorder | **Type of Submission:** 505(b)(2) Original New Drug Application | |
| **Dosage form/ strengths** | Extended Release Tablet/ 50 mg/tablet and 100 mg/tablet | | |
| **Route of Administration** | Oral | | |

## SUMMARY

***Submission:*** This 505(b)(2) New Drug Application is for an extended release (ER) film coated desvenlafaxine tablet indicated for the treatment of major depressive disorder. The proposed drug product tablets contain desvenlafaxine fumarate monohydrate equivalent to 50 mg or 100 mg desvenlafaxine free base per tablet. The proposed product is a (b) (4) based drug product, formulated to exhibit extended release properties. This application is an electronic NDA, filed as a 505(b)(2) application, with Pristiq® (NDA 21992) as the listed drug. Pristiq® contains desvenlafaxine succinate monohydrate instead of desvenlafaxine fumarate monohydrate as the active ingredient.

***Review:*** The Biopharmaceutics review for this NDA is being focused on the evaluation and acceptability of the following:
1) Proposed dissolution methodology,
2) Proposed dissolution acceptance criteria,
3) In vitro alcohol dose dumping study, and
4) Information supporting the extended release claim

## RECOMMENDATION:

ONDQA-Biopharmaceutics has evaluated the information provided in NDA 205583 and concludes the following:

- The dissolution method and acceptance criteria, as summarized below, are acceptable on an interim basis:

  Interim dissolution method:
  USP Apparatus I (basket)
  Temperature: 37°C
  Rotation speed: 100 rpm
  Medium: 900 mL 0.1 N HCl

  Interim dissolution acceptance criteria:
  - 2 hours: (b) (4)%
  - 4 hours: %
  - 8 hours: %
  - 16 hours: NLT (b) (4)%

  The following post marketing commitment (PMC) comments should be communicated as appropriate to the Applicant:
  - *Develop an optimal discriminating dissolution method that can distinguish between batches of drug product that were bioequivalent to the listed drug and batches that were no bioequivalent to the listed drug for both the 50 mg and the 100 mg strengths.*
  - *Within one year of NDA approval, submit a supplement to the NDA containing a dissolution method development report with all the necessary information used to select the new dissolution method, including raw data, tables, and figures, clearly stating all the testing conditions used for each data set.*
  - *Using the new discriminating dissolution method, set the acceptance criteria using the dissolution data from at least six batches (n=12) of 50 mg and 100 mg drug product. The selected dissolution acceptance criteria should reject those batches that were not bioequivalent to the reference listed drug.*

- In vitro alcohol dose dumping study:
  Dose dumping in the presence of alcohol does not occur in vitro.

- Extended release claim:
  The extended release claim for the proposed drug product is acceptable.

From the Biopharmaceutics perspective, NDA 205583 for Desvenlafaxine Extended Release Tablets (50 mg/tablet and 100 mg/tablet) is recommended for **APPROVAL with a PMC**.

**Elsbeth Chikhale, Ph.D.**
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

**Angelica Dorantes, Ph.D.**
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

## BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES

### SUBMISSION:

This 505(b)(2) New Drug Application is for an extended release film coated desvenlafaxine tablet indicated for the treatment of major depressive disorder. Desvenlafaxine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). Desvenlafaxine ER Tablets 50 mg and 100 mg have [redacted] (b) (4) The drug product was designed to be bioequivalent to Pristiq®. This application is an electronic NDA, filed as a 505(b)(2) application, with Pristiq® (NDA 21992) as the listed drug, however, instead of using the desvenlafaxine succinate monohydrate used in the listed drug as the drug substance this Applicant (Sun Pharmaceuticals) chose to use the desvenlafaxine fumarate monohydrate. Based on reported permeability and solubility data, desvenlafaxine is considered a Biopharmaceutical Classification System (BCS) Class III compound by the Applicant. However, no official BCS class assignment has been requested in this NDA.

### BIOPHARMACEUTICS INFORMATION:

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the following:
1) Proposed dissolution methodology,
2) Proposed dissolution acceptance criteria,
3) In vitro alcohol dose dumping study, and
4) Information supporting the extended release claim

### DRUG PRODUCT FORMULATION DEVELOPMENT:

The developmental formulations of desvenlafaxine ER 100 mg tablets, were evaluated in the preliminary bioequivalence (BE) studies. The developmental batches were formulated to optimize the levels of [redacted] (b) (4). The concentrations (% w/w) and [redacted] (b) (4) Because fumarate is highly [redacted] (b) (4) tablet weights of the final formulation were [redacted] (b) (4)

The following developmental formulations were used during the drug product formulation development:

**Comparison of Compositions of Developmental Formulations, 100 mg and 50 mg**

| Ingredients | Batch No. 10712869BB002 | Batch No. 10712869BB003 | Batch No. JKK4236* | Batch No. 10712868DT010 |
|---|---|---|---|---|
| | 100mg | | | 50mg |
| | mg/tab | | | |
| (b) (4) | | | | |
| Desvenlfaxine Fumarate | 144.07 | 144.07 | 144.07 | 72.04 |
| Microcrystalline Cellulose (b) (4) | | | | (b) (4) |
| Hypromellose (b) (4) (b) (4) | | | | |
| (b) (4) | | | | |
| Magnesium Stearate (b) (4) (b) (4) (b) (4 | | | | |
| Talc | | | | |
| Colloidal Silicon Dioxide (b) (4 | | | | |
| (b) (4) | | | | |

* This is a scale up batch that is the same formulation as the proposed formulation with the exception of a different ratio of (b) (4) not present in the final formulation. Results of the study done with this batch are grouped with those of the final formulation.

The table below lists the BE studies that used developmental formulations. The developmental formulations, 10712869BB002 and 10712868DT010 are not bioequivalent to the listed drug. The developmental formulation, 10712869BB003 is bioequivalent to the listed drug under fasting conditions, but it is not bioequivalent under fed conditions. However, note that if an outlier subject is removed, formulation 10712869BB003 is bioequivalent under fed conditions. The final to-be-marketed formulations for the 50 mg and the 100 mg strength are bioequivalent to the listed drug under fed and fasted conditions.

**BE studies using Desvenlafaxine 100mg and 50mg Developmental Formulations**

| Study Number (Dates of Conduct) | No. (Completed) Age (yrs) BMI (kg/m$^2$) | Design | Dosing Condition | Desvenlafaxine Treatments | Batch Number |
|---|---|---|---|---|---|
| **100 mg** | | | | | |
| PKD_11_033 (02 Feb – 14 Feb 2011) | 20 (18) 30.9±7.38 21.49±2.092 | A randomized, open label, two treatment, single dose, crossover, BE study with a 7-day wash out period | Fasted | Desvenlafaxine 100 mg ER Tablets | (b) (4) |
| | | | | Pristiq® 100 mg ER Tablets | E27888 |
| PKD_11_034 (02 Feb – 14 Feb 2011) | 20 (20) 33.1±7.50 21.67±2.215 | A randomized, open label, two treatment, single dose, crossover, BE study with a 7-day wash out period | Fed | Desvenlafaxine 100 mg ER Tablets | (b) (4) |
| | | | | Pristiq® 100 mg ER Tablets | E27888 |
| PKD_11_271 (21 June – 03 July 2011) | 20 (15) 31.9±5.83 21.54±1.686 | A randomized, open label, two treatment, single dose, crossover, BE study with a 7-day wash out period | Fasted | Desvenlafaxine 100 mg ER Tablets | (b) (4) |
| | | | | Pristiq® 100 mg ER Tablets | E70999 |
| PKD_11_272 (21 June – 03 July 2011) | 20 (19) 33.1±6.21 22.29±2.132 | A randomized, open label, two treatment, single dose, crossover, BE study with a 7-day wash out period | Fed | Desvenlafaxine 100 mg ER Tablets | (b) (4) |
| | | | | Pristiq® 100 mg ER Tablets | E70999 |
| **50 mg** | | | | | |
| PKD_11_348 (11 Oct – 22 Oct 2011) | 12 (12) 32.8±7.18 21.55±1.579 | A randomized, open label, two treatment, single dose, crossover, BE study with a 7-day wash out period | Fasted | Desvenlafaxine 50 mg ER Tablets | (b) (4) |
| | | | | Pristiq® 50 mg ER Tablets | E89895 |

The following table lists the BE studies in which the final to-be-marketed 50mg and 100 mg formulations are BE to the listed drug, Pristiq®

**BE studies using Desvenlafaxine 100mg and 50mg Final Formulations**

| Study Number (dates of conduct) | No. (completed) Age (yrs) BMI (kg/m$^2$) | Design | Desvenlafaxine Fumarate Treatment | Batch Number |
|---|---|---|---|---|
| **Pilot Study** | | | | |
| PKD_11_382 19 Nov – 30 Nov 2011 | 16 (15) 30.1±4.70 21.59±1.834 | A randomized, open label, two treatment, single dose, crossover, BE study with a 7-day wash out period under fasting conditions | Desvenlafaxine 100 mg ER Tablets | JKK4236 |
| | | | Pristiq® 100 mg | Lot E70999 |
| **Pivotal Studies** | | | | |
| PKD_12_170 28 May – 16 June 2012 | 36 (32) 33.5 ± 6.98 22.01 ± 1.730 | Randomized, open label, three treatment, three period, six sequence, single dose bioequivalence study under fasting and fed conditions | Desvenlafaxine, 100 mg | Batch JKL1223A |
| | | | Pristiq® 100 mg (fasting) | Lot E70999 |
| PKD_12_171 04 Aug – 16 Aug 2012 | 50 (47) 32.5 ± 6.27 21.79 ± 2.033 | Randomized, open label, two treatment, two period, two sequence, single dose, crossover bioequivalence study under fasting conditions | Desvenlafaxine, 50 mg | Batch JKL1641A |
| | | | Pristiq® 50 mg | Lot E89895 |

The composition of the proposed final to-be-marketed 50 mg and 100 mg tablets is presented below.

**Composition of the Desvenlafaxine 100mg and 50mg Final Formulations**

| Ingredient | Function | mg/unit (50 mg) | mg/unit (100 mg) |
|---|---|---|---|
| (b) (4) | | | |
| Desvenlafaxine Fumarate | Active | 72.035 | 144.070 |
| Hypromellose (b) (4) USP | | | (b) (4) |
| (b) (4) | | | |
| Microcrystalline Cellulose (b) (4) | | | |
| Magnesium Stearate, NF | | | |
| Ferric Oxide Red[2] | | | |
| (b) (4) | | | |
| Talc, USP | | | |
| (b) (4) | | | |
| Colloidal silicon Dioxide, NF | | | |
| **Film-Coating** | | | |
| (b) (4) | | | (b) (4) |
| Hypromellose (b) (4) USP | | | |
| Titanium Dioxide, USP | | | |
| PEG (b) (4) NF | | | |
| Talc, USP | | | |
| Ferric Oxide Red[2], NF | | | |
| Ferric Oxide Yellow[2], NF | | | |
| (b) (4) | | | |
| **Total Weight of Coated Tablets:** | | 463.500 | 463.500 |

(b) (4)

7 Page(s) have been Withheld in Full as b4 (CCI/ TS) immediately following this page

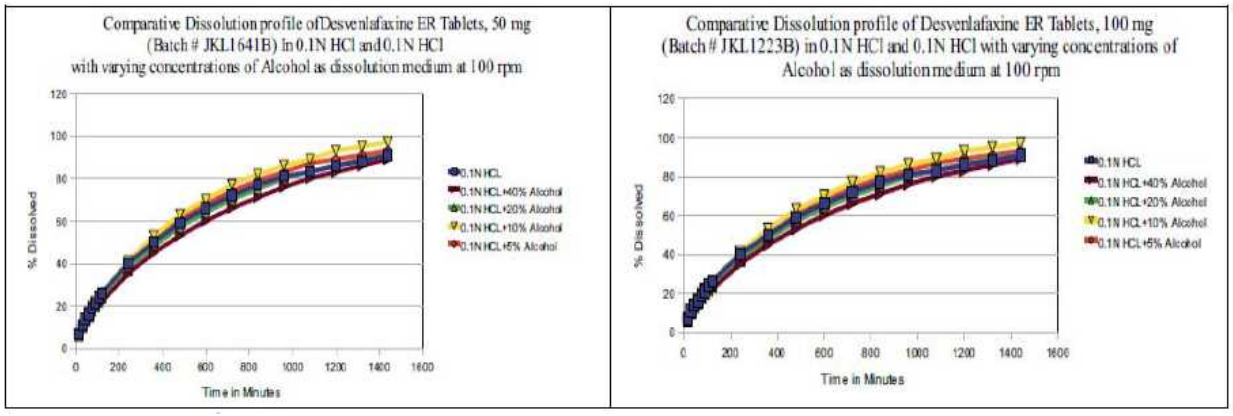
(b) (4)

**ALCOHOL DOSE-DUMPING:**

The Applicant has performed a dissolution study in media of various concentrations of alcohol to determine whether or not the proposed product exhibits "dose-dumping". Sampling was conducted after 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hours. Testing was performed using 0.1 N HCl as the control. The following alcohol concentrations were studied:

- Control (0.1 N HCl)
- 5% v/v alcohol in 0.1 N HCl
- 10% v/v alcohol in 0.1 N HCl
- 20% v/v alcohol in 0.1 N HCl
- 40% v/v alcohol in 0.1 N HCl

**Comparative Dissolution Profiles of Desvenlafaxine ER Tablets, 50 mg and 100 mg in 0.1 N HCl and 0%, 5%, 10%, 20% and 40% v/v Alcohol**




The $f_2$ values for the mean dissolution values were comparable across all alcohol concentrations demonstrating that dose-dumping does not occur with the proposed formulation of desvenlafaxine ER tablets. All $f_2$ values were above 50, showing that concentrations of alcohol up to 40% do not affect the *in vitro* dissolution of Desvenlafaxine ER tablets of either strength.

***Reviewer's Assessment of the alcohol dose-dumping study:***
*The provided information demonstrates that the drug does not dose-dump in vitro with alcohol concentrations up to 40% compared to without alcohol.*

**EXTENDED RELEASE CLAIM:**

The proposed 50 mg and 100 mg tablets are bioequivalent to the approved 50 mg and 100 mg Pristiq® extended release tablets, and both products have a comparable half-life of 9-10 hours. Therefore, ***the extended release claim for the proposed drug product is acceptable.***

**RECOMMENDATION:**

- The dissolution method and acceptance criteria, as summarized below, are acceptable on an interim basis:

  Interim dissolution method:
  USP Apparatus I (basket)
  Temperature: 37°C
  Rotation speed: 100 rpm
  Medium: 900 mL 0.1 N HCl

  Interim dissolution acceptance criteria:
  - 2 hours: (b) (4)%
  - 4 hours: %
  - 8 hours: %
  - 16 hours: NLT (b) (4)%

The following post marketing commitment (PMC) comments should be communicated as appropriate to the Applicant:

- *Develop an optimal discriminating dissolution method that can distinguish between batches of drug product that were bioequivalent to the listed drug and batches that were no bioequivalent to the listed drug for both the 50 mg and the 100 mg strengths.*
- *Within one year of NDA approval, submit a supplement to the NDA containing a dissolution method development report with all the necessary information used to select the new dissolution method, including raw data, tables, and figures, clearly stating all the testing conditions used for each data set.*
- *Using the new discriminating dissolution method, set the acceptance criteria using the dissolution data from at least six batches (n=12) of 50 mg and 100 mg drug product. The selected dissolution acceptance criteria should reject those batches that were not bioequivalent to the reference listed drug.*

- In vitro alcohol dose dumping study:
  Dose dumping in the presence of alcohol does not occur in vitro.

- Extended release claim:
  The extended release claim for the proposed drug product is acceptable.

From the Biopharmaceutics perspective, NDA 205583 for Desvenlafaxine Extended Release Tablets (50 mg/tablet and 100 mg/tablet) is recommended for **APPROVAL with a PMC**.

---

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

---

/s/

---

ELSBETH G CHIKHALE
12/13/2013

ANGELICA DORANTES
12/13/2013

**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** | **205583** | **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** | **3/25/13** | **Route of Administration** | **Oral** |
| **Estimated Due Date of OCP Review** | **12/21/13** | **Sponsor** | **Sun Pharmaceuticals** |
| **Medical Division Due Date** | **12/28/13** | **Priority Classification** | **Standard** |
| **PDUFA Due Date** | **1/28/14** | | |
| | | | |

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


***Summary***

The sponsor has developed a Desvenlafaxine fumarate extended release (ER) tablets with the strengths equivalent to 50 mg and 100 mg free base and is seeking approval via the 505(b)(2) route. The sponsor is cross referencing Pristiq (Desvenlafaxine Succinate) by Pfizer, which is approved for major depressive disorder. Pristiq is available in 50 mg and 100 mg ER tablets. Clinical studies for Pristiq were conducted using doses from 50 to 400 mg and showed no clinical advantage of the higher doses over 50 mg. Therefore, the recommended dosing for Pristiq is 50 mg once daily.

The NDA is dependent on 6 pilot and 2 pivotal bioequivalent studies. Five of the pilot studies used developmental formulations. One pilot and 2 pivotal studies used the final formulation. The following are the pivotal studies:

Study No. PKD-12-170: A Randomized, open label, three treatment, three period, six sequence, single dose, crossover bioequivalence study comparing SUN's Desvenlafaxine 100 mg ER tablets when administered under fasting and fed conditions and Pristiq (Desvenlafaxine) 100 mg ER Tablet by Wyeth when administered under fasting condition in healthy human adult subjects

Study No. PKD-12-171: A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Desvenlafaxine 50mg Extended Release tablets of SUN Pharmaceutical Industries Limited, and Pristiq® (Desvenlafaxine) 50mg Extended Release tablets of Wyeth Pharmaceutical Industries Limited in healthy human subjects .


***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** | **8** | | |
| **HPK Summary** | **x** | | | |
| **Labeling** | **x** | | | |
| **Reference Bioanalytical and Analytical Methods** | **x** | **5** | | **Bioanalytical Reports** |
| **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** | **8** | | |
| multiple dose: | | | | |
| **Patients-** | | | | |
| single dose: | | | | |

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

| | | | | |
|---|---|---|---|---|
| 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** | **8** | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies** | **x** | | | |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | **x** | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | **8** | | | |
| | | | | |

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 the analytical assay? | x | | | |

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

| | | | | | |
|---|---|---|---|---|---|
| 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.

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

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

| | | |
|---|---|---|
| Reviewing Clinical Pharmacologist | Kofi Kumi, Ph.D. | Date 5/6/13 |
| Team Leader/Supervisor | Hao Zhu, Ph.D. | Date 5/6/13 |

---

**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
05/09/2013

HAO ZHU
05/09/2013

# PRODUCT QUALITY - BIOPHARMACEUTICS
# FILING REVIEW

| | |
|---|---|
| **NDA Number** | 205583 |
| **Submission Date** | 3/28/13 |
| **Product name, generic name of the active** | Desvenlafaxine ER Tablets |
| **Dosage form and strength** | Extended Release Tablets - 50 mg/tablet and 100 mg/tablet |
| **Route of Administration** | Oral |
| **Applicant** | Sun Pharma Global FZE, United Arab Emirates |
| **Clinical Division** | Division of Psychiatry Products |
| **Type of Submission** | Original NDA – 505(b)(2) |
| **Biopharmaceutics Reviewer** | Elsbeth Chikhale, Ph.D. |
| **Biopharmaceutics Team Leader** | Angelica Dorantes, Ph.D. |

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full Biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

**ONDQA-BIOPHARMACEUTICS**
**A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING

| | Parameter | Yes | No | Comment |
|---|---|---|---|---|
| 1. | Does the application contain dissolution data? | x | | |
| 2. | Is the dissolution test part of the DP specifications? | x | | Proposed method: Apparatus 1 (basket), 900 mL of 0.1 N HCl at 37 °C, at 100 rpm<br>Proposed acceptance criteria:<br>· 2 hour: (b) (4) %<br>· 4 hours: (b) (4) %<br>· 8 hours: %<br>· (b) (4) hours: (b) (4) %<br>· hours: NLT (b) (4) % |
| 3. | Does the application contain data to support the proposed dissolution acceptance criteria | x | | Section 3.2.P.5.6 |
| 4. | Does the application contain the dissolution method development report? | x | | Section 2.7.1 and 3.2.P.5.6 |
| 5. | Does the application contain data on the discriminating ability of the dissolution method | x | | |
| 6. | Is there a validation package for the analytical method and dissolution methodology? | x | | Section 3.2.P.5.3 and 3.2.P.5.6 |
| 7. | Does the application include a biowaiver request? | | x | Not needed |
| 8. | Does the application include an IVIVC model? | | x | Not applicable |

| | | | | |
|---|---|---|---|---|
| 9. | Is information such as BCS classification mentioned, and supportive data provided? | | x | Not applicable |
| 10. | Is information on mixing the product with foods or liquids included? | | x | Not applicable |
| 11. | Is there any in *vivo* BA or BE information in the submission? | x | | Relative bioavailability studies of the proposed 50 and 100 mg ER tablet versus the RLD 50 and 100 mg ER tablet were conducted. The studies will be reviewed by OCP. |
| 12. | Does the application include in *vitro* alcohol interaction studies? | x | | Section 2.7.1 |
| **B. FILING CONCLUSION** | | | | |
| | **Parameter** | **Yes** | **No** | **Comment** |
| 13. | **IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?** | x | | |
| 14. | If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant. | | | Not applicable |
| 15. | If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant. | | | Not applicable |
| 16. | Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter? | x | | |

SUBMISSION:

This 505(b)(2) New Drug Application is proposing Desvenlafaxine Extended Release (ER) Tablets containing either 50 mg or 100 mg (base equivalents) of desvenlafaxine fumarate monohydrate for the treatment of major depressive disorder. Desvenlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI), was first approved in February 2008 as Pristiq® (NDA 21992), the reference listed drug (RLD), which contains the succinate salt of the active moiety. The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of 1) the proposed dissolution methodology, 2) dissolution acceptance criteria, 3) the in vitro alcohol dose dumping study, and 4) the extended release claim.

# PRODUCT QUALITY - BIOPHARMACEUTICS
# FILING REVIEW

RECOMMENDATION:
ONDQA-Biopharmaceutics has reviewed NDA 205583 for filing purposes and we found this NDA filable from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

*{See appended electronic signature page}*
Elsbeth Chikhale, Ph.D. 5/9/13
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

*{See appended electronic signature page}*
Angelica Dorantes, Ph.D. 5/9/13
Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

---

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

---

/s/

---

ELSBETH G CHIKHALE
05/09/2013

ANGELICA DORANTES
05/09/2013

# PRODUCT QUALITY - BIOPHARMACEUTICS
# FILING REVIEW

| | |
|---|---|
| **NDA Number** | 205583 |
| **Submission Date** | 3/28/13 |
| **Product name, generic name of the active** | Desvenlafaxine ER Tablets |
| **Dosage form and strength** | Extended Release Tablets - 50 mg/tablet and 100 mg/tablet |
| **Route of Administration** | Oral |
| **Applicant** | Sun Pharma Global FZE, United Arab Emirates |
| **Clinical Division** | Division of Psychiatry Products |
| **Type of Submission** | Original NDA – 505(b)(2) |
| **Biopharmaceutics Reviewer** | Elsbeth Chikhale, Ph.D. |
| **Biopharmaceutics Team Leader** | Angelica Dorantes, Ph.D. |

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full Biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

**ONDQA-BIOPHARMACEUTICS**
**A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING**

| | Parameter | Yes | No | Comment |
|---|---|---|---|---|
| 1. | Does the application contain dissolution data? | x | | |
| 2. | Is the dissolution test part of the DP specifications? | x | | Proposed method: Apparatus 1 (basket), 900 mL of 0.1 N HCl at 37 °C, at 100 rpm<br>Proposed acceptance criteria:<br>· 2 hour: (b) (4)%<br>· 4 hours: (b) (4)%<br>· 8 hours: %<br>· (b) (4) hours: (b) (4)%<br>· hours: NLT (b) (4)% |
| 3. | Does the application contain data to support the proposed dissolution acceptance criteria | x | | Section 3.2.P.5.6 |
| 4. | Does the application contain the dissolution method development report? | x | | Section 2.7.1 and 3.2.P.5.6 |
| 5. | Does the application contain data on the discriminating ability of the dissolution method | x | | |
| 6. | Is there a validation package for the analytical method and dissolution methodology? | x | | Section 3.2.P.5.3 and 3.2.P.5.6 |
| 7. | Does the application include a biowaiver request? | | x | Not needed |
| 8. | Does the application include an IVIVC model? | | x | Not applicable |

# PRODUCT QUALITY - BIOPHARMACEUTICS
# FILING REVIEW

| | | | | |
|---|---|---|---|---|
| 9. | Is information such as BCS classification mentioned, and supportive data provided? | | x | Not applicable |
| 10. | Is information on mixing the product with foods or liquids included? | | x | Not applicable |
| 11. | Is there any in *vivo* BA or BE information in the submission? | x | | Relative bioavailability studies of the proposed 50 and 100 mg ER tablet versus the RLD 50 and 100 mg ER tablet were conducted. The studies will be reviewed by OCP. |
| 12. | Does the application include in *vitro* alcohol interaction studies? | x | | Section 2.7.1 |

**B. FILING CONCLUSION**

| | Parameter | Yes | No | Comment |
|---|---|---|---|---|
| 13. | **IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?** | x | | |
| 14. | If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant. | | | Not applicable |
| 15. | If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant. | | | Not applicable |
| 16. | Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter? | x | | |

SUBMISSION:

This 505(b)(2) New Drug Application is proposing Desvenlafaxine Extended Release (ER) Tablets containing either 50 mg or 100 mg (base equivalents) of desvenlafaxine fumarate monohydrate for the treatment of major depressive disorder. Desvenlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI), was first approved in February 2008 as Pristiq® (NDA 21992), the reference listed drug (RLD), which contains the succinate salt of the active moiety. The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of 1) the proposed dissolution methodology, 2) dissolution acceptance criteria, 3) the in vitro alcohol dose dumping study, and 4) the extended release claim.

# PRODUCT QUALITY - BIOPHARMACEUTICS
# FILING REVIEW

RECOMMENDATION:
ONDQA-Biopharmaceutics has reviewed NDA 205583 for filing purposes and we found this NDA filable from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

*{See appended electronic signature page}*
Elsbeth Chikhale, Ph.D. 5/9/13
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

*{See appended electronic signature page}*
Angelica Dorantes, Ph.D. 5/9/13
Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

---

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

---

/s/

---

ELSBETH G CHIKHALE
05/09/2013

ANGELICA DORANTES
05/09/2013



Reference ID: 3449781