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MEDICAL REVIEW(S)

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Established Name Desvenlafaxine Fumarate
Extended Release Tablets
(Proposed) Trade Name Desvenlafaxine Extended
Release Tablets
Therapeutic Class SNRI
Applicant Sun Pharma Global FZE,
United Arab Emirates

Formulation(s) Extended Release Tablets
Dosing Regimen 50 mg, 100 mg
Indication(s) Major Depressive Disorder
(MDD)
Intended Population(s) Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that the Division take an Approval action for this 505(b)(2) NDA 205583. Sun Pharmaceutical has submitted two pivotal bioequivalence studies that demonstrate that Desvenlafaxine Extended Release Tablets (desvenlafaxine fumarate) is bioequivalent to the reference listed drug, Pristiq[®] (desvenlafaxine succinate), in the fasting state.

In the fed state, C_{max} increased by about 37% and AUC increased by 29% for Desvenlafaxine Extended Release Tablets. For Pristiq[®], C_{max} increased by only 16% in the fed state. AUC was similar for Pristiq[®] in the fasted and fed states. The USPI for Pristiq[®] states that Pristiq[®] can be administered with or without food. This 21% increase (37%-16%) in C_{max} and 29% increase in AUC in the fed state for Desvenlafaxine Extended Release Tablets compared to Pristiq[®] (RLD) were discussed extensively by the clinical and OCP teams. The consensus was that this difference would not be clinically significant and that it would be safe to administer Desvenlafaxine Extended Release Tablets with or without food. This decision was further supported by the observation that the adverse events in the pivotal studies almost exclusively occurred when Desvenlafaxine Extended Release Tablets were administered in the fasting state.

1.2 Risk Benefit Assessment

The bioequivalence studies were brief in duration and subjects were healthy volunteers. Efficacy was not evaluated. Safety data were limited. Based on the limited data, the risk benefit appears to be similar to the reference listed drug, Pristiq[®].

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine risk minimization (i.e., FDA-approved product label) and routine pharmacovigilance will be adequate to manage the risk-benefit profile of Desvenlafaxine Extended Release Tablets in the treatment of MDD in adults.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements and commitments are recommended at this time from a clinical perspective.

Dr. Bhamidipati (ONDQA-DNDQA1) stated that a Postmarketing Commitment will be discussed with the applicant and finalized prior to approval of this NDA. The

Postmarketing Commitment would involve changing the desiccant content for 30-Count packaging configuration due to the observed stability trends (b) (4).

Dr. Elsbeth Chikhale (ONDQA-Biopharmaceutics) has requested that the following Postmarketing Commitment be communicated 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 not 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.*

2 Introduction and Regulatory Background

2.1 Product Information

Desvenlafaxine (O-desmethylvenlafaxine), a serotonin and norepinephrine reuptake inhibitor (SNRI), is the major active metabolite of the antidepressant, venlafaxine. Desvenlafaxine succinate monohydrate was originally approved by FDA in February 2008 as Pristiq® (NDA 021-992) for the treatment of major depressive disorder (MDD) in adults. Pristiq® is available in 50 mg and 100 mg strength tablets, which are both designated as the Reference Listed Drug (RLD). The recommended dose is 50 mg once daily, with or without food, although higher doses are also used (up to 400 mg/day in clinical trials).

Sun has developed Desvenlafaxine Extended Release Tablets, available in strengths equivalent to 50 mg and 100 mg of desvenlafaxine (as the free base). Desvenlafaxine Extended Release Tablets are intended for the treatment of adults with MDD, the same indication as Pristiq®. Dosage and administration instructions proposed for Desvenlafaxine Extended Release Tablets are the same as those for the RLD.

The proposed tablets contain a new salt of the active moiety, desvenlafaxine fumarate. According to the Applicant, the alternate salt form used in Sun's proposed product does not lead to a change in the pharmacokinetics and therefore the pharmacodynamic or toxicity characteristics of the active moiety. The current Pristiq® label states that "in clinical studies, doses of 50 mg to 400 mg per day were shown to be effective." At this highest daily dose (400 mg/day), approximately 576 mg of fumaric acid would be

ingested with the proposed product. Fumaric acid (and its calcium, magnesium, potassium, and sodium salts) is approved for use as a food additive (21 CFR 172.350). Fumarate salts have also been approved for other drug products. For example, at the highest recommended dose for quetiapine (800 mg/day), the amount of fumaric acid ingested is 922 mg/day.

2.2 Currently Available Treatments for Proposed Indications

Currently available approved treatments for MDD include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), bupropion, trazodone, mirtazapine, and electroconvulsive therapy (ECT). Several psychotherapeutic modalities have also been reported to be efficacious in patients with MDD and are frequently used in combination with medications.

2.3 Availability of Proposed Active Ingredient in the United States

Desvenlafaxine Extended Release Tablets (desvenlafaxine fumarate) is a new drug under development for licensing by the applicant and is currently not marketed in the United States.

Pristiq® Extended Release Tablets (desvenlafaxine succinate), the Reference Listed Drug (RLD) for this 505(b)(2) application, is readily available in the United States. Pristiq® has received marketing authorization in 45 countries and is currently marketed in 37 countries. The cumulative worldwide marketing exposure to desvenlafaxine succinate sustained release (DVS SR) from 12 May 2008 (date of first marketing) through 28 February 2013 is estimated to be 1,945,464 patient-years.¹

2.4 Important Safety Issues With Consideration to Related Drugs

Some safety issues associated with the use of SNRIs include elevated blood pressure, increased risk of bleeding in conjunction with the use of aspirin or nonsteroidal anti-inflammatory drugs, serotonin syndrome, discontinuation syndrome, activation of mania/hypomania, seizure, and increased risk of suicide in children/adolescents/young adults.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A Type B pre-IND meeting (IND 113361) was scheduled with the Division of Psychiatry Products on 7 November 2011 to discuss the development program. FDA preliminary responses were provided before the meeting. As no issues required clarification, the meeting was subsequently cancelled by the Applicant.

¹ From Pristiq DSUR (3/1/12-2/28/13), p.3

2.6 Other Relevant Background Information

(b) (4)

In the filing letter (29 May 2013), the Agency informed the Applicant that under PREA, “all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.” The Agency denied the request for a (b) (4) of pediatric studies for this application (b) (4)

Therefore, Sun Pharma then submitted an *Amendment to Filing Communication* (17 June 2013) with a revised pediatric deferral request. Sun Pharma is now requesting a deferral of the need to conduct pediatric studies with Desvenlafaxine Fumarate Extended Release Tablets under PREA in children and adolescents ages 7 to 17 years. Sun Pharma is requesting this deferral because the studies in adults are complete and this product will be ready for approval for use in adults before pediatric studies will be complete.

The following is an excerpt from the proposed Sun Pharma Pediatric Study Plan:

Sun Pharma plans to conduct the following study to assess the efficacy and safety of Desvenlafaxine Fumarate Extended Release Tablets for the treatment of MDD in children and adolescents ages 7 to 17 years:

- *A double-blind, placebo-controlled, 8-week, safety and efficacy study in children and adolescents ages 7 to 17 years with MDD. If the basis for dosing is not available from the published literature, Sun Pharma will plan to conduct the appropriate studies to establish the doses to be used in the Phase 3 study.*

Sun Pharma is proposing the following milestones for this Phase 3 study:

- a. Submission of the final pediatric protocol: 2 years after approval (28 January 2016)*
- b. Study Initiation date: 1 year after submission of final protocol (28 January 2017)*
- c. Submission of final study reports: 3 years to complete study and 1 year to prepare report (28 January 2021)*

Sun Pharma continues to request a partial waiver of the need to conduct pediatric studies with Desvenlafaxine Fumarate Extended Release Tablets under PREA in children ages 0 to 6 years. Sun Pharma is requesting this waiver because studies are highly impracticable since MDD cannot be reliably diagnosed in children in this age group. The Applicant notes that in the filing letter (29 May 2013) for this NDA, the Agency indicated that a waiver in this population on this basis would be granted.

Sun's Pediatric Plan was reviewed by PeRC on 12/4/2013.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No problems with data quality or integrity were identified. The submission was organized and electronic navigation was not difficult.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all studies were performed according to Good Clinical Practice (GCP) and with the approval of the Drugs Controller General of India (DCGI).

Sun Pharma Global certified that it did not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this NDA.

The Division requested an OSI Consult (5/8/2013) for routine Biopharmaceutical Inspections (BE) of the following clinical and analytic sites:

Table 1: Clinical and Analytic Sites

Clinical Site	Analytical Site
Facility Name: SUN Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 (India) (Tel): 91-265-2350789, 91-265-6615500	Facility Name: SUN Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 (India) (Tel) + 91-265-2350789, 91-265-6615500
Clinical Investigator: Aman Khanna, MD	Principal Analytical Investigator: K. Shivram, Ph.D.

Source: OSI Consult

The Division requested that the inspections be conducted and that the Inspection Summary Results be provided by 11/21/2013. The final inspection reports are currently pending. Dr. Shin-Ye Chang (DPP Regulatory Project Manager) spoke with the OSI BE inspector on 12/16/2013. The inspector stated that the inspection has been completed and that no major issues were identified. A 483 was issued but it will not affect approval.

3.3 Financial Disclosures

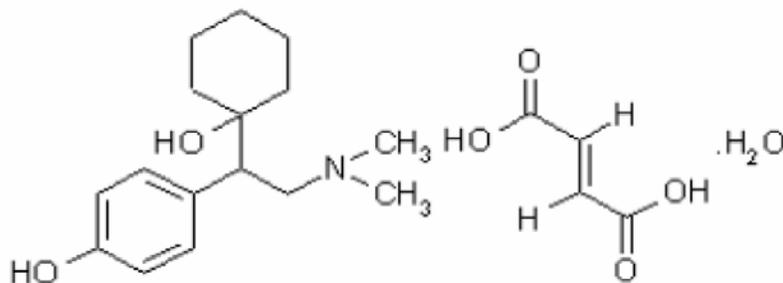
The Applicant certified that the Applicant had not entered into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that each clinical investigator required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b) did not disclose any such interests. The Applicant further certified that no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(1).

4 Significant Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Desvenlafaxine fumarate is a white to off-white hygroscopic powder that is slightly soluble in water. Its chemical name is (\pm)-4-[2-dimethylamino-1-(1-hydroxycyclohexyl)ethyl]-phenol fumarate monohydrate (salt). The molecular weight of desvenlafaxine fumarate is 397.46 g/mol and the empirical formula is C₁₆H₂₅NO₂ (free base) and C₁₆H₂₅NO₂•C₄H₄O₄•H₂O (fumarate monohydrate).

Figure 1 : Structure of Desvenlafaxine Fumarate
Structure of Desvenlafaxine Fumarate



The solubility of the fumarate salt of desvenlafaxine in water is 8.75 mg/mL, less than that of the succinate salt (64.6 mg/mL).

In Vitro Dissolution

The Office of Generic Drugs (OGD) recommends 0.9% sodium chloride as the proposed dissolution medium for extended-release desvenlafaxine products. However, Desvenlafaxine ER Tablets are less than $\frac{(b)}{(4)}$ % dissolved in $\frac{(b)}{(4)}$ hours in this medium. Therefore, 0.1 N hydrochloric acid (HCl) was chosen as the dissolution medium by the Applicant. Desvenlafaxine ER Tablets (50 and 100 mg) have been shown to have similar *in vitro* dissolution profiles to corresponding strengths of the reference product,

Pristiq® (50 mg and 100 mg), when tested using the proposed release/stability method 0.1 N HCl f_2 (b) (4). The profiles were not similar in the other media tested (b) (4).

Dose Dumping in Alcohol

Sun has performed an *in vitro* dissolution study using various concentrations of alcohol (0, 5, 10, 20, and 40%) added to the dissolution medium to determine whether or not the proposed product exhibits “dose-dumping”. Based on feedback from the Division in the form of preliminary responses received on 3 November 2011, testing was performed in the optimum medium, 0.1 N HCl, and included frequent sampling timepoints (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). Twelve dosage units of each strength were tested. All f_2 values were well above 50, demonstrating that concentrations of alcohol up to 40% do not affect the *in vitro* dissolution of Desvenlafaxine ER tablets of either strength.

Summary of ONDQA-DNDQA1 Review

Dr. Shastri Bhamidipati of the Division of New Drug Quality Assessment (ONDQA) reviewed this NDA. Dr. Bhamidipati stated that this NDA for Desvenlafaxine Extended Release Tablets of 50 and 100 mg strength is recommended for approval based on Chemistry, Manufacturing and Controls information submitted in the application. In addition, the Office of Compliance has provided an overall acceptable recommendation for all the manufacturing sites for this NDA in EES (Establishment Evaluation System).

Dr. Bhamidipati stated that a Post Marketing Commitment will be discussed with the applicant and finalized prior to approval of this NDA. The Post Marketing Commitment would involve changing the desiccant content for 30-Count packaging configuration due to the observed stability trends (b) (4) as described in Dr. Bhamidipati’s review:

Stability data for three pilot scale batches of 50 mg and 100 mg Desvenlafaxine Extended-Release Tablets packaged in HDPE bottles of 30, 90 and 1000 count packaging configurations stored at long term (25°C/65% RH) and accelerated (40°C/75% RH) conditions were provided up to 12 months and 6 months respectively. The applicant claimed that there were no observable trends in any of the quality attributes monitored on stability and proposed a (b) (4) month shelf life for the drug product. However, review of stability data showed (b) (4) increase on storage and a noticeable decrease in assay content for 50 mg strength tablets both of which were more pronounced in 30 count presentation relative to the 90 and 1000 count presentations.

Therefore, ONDQA is recommending a shelf-life of 12 months for expiration dating of the drug product based on long term storage stability data submitted. This shelf-life may

be extended pending verification of the applicant's response regarding observed stability trends for the 50 mg 30-count presentation.

Summary of ONDQA-Biopharmaceutics Review

Dr. Elsbeth Chikhale concluded that 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: (b) (4) %
- 8 hours: (b) (4) %
- 16 hours: NLT (b) (4) %

Dr. Elsbeth Chikhale requested that the following post marketing commitment (PMC) comments be communicated 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 not 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.*

Dr. Chikhale concluded from the *in vitro* alcohol dose dumping study that dose dumping in the presence of alcohol does not occur *in vitro*.

Finally, Dr. Chikhale concluded that he extended release claim for the proposed drug product is acceptable and that 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**.

4.2 Microbiology

Dr. Erika Pfeiler, a microbiologist in ONDQA, reviewed the product quality microbiology assessment (submitted 28 March 2013) of microbial limits for Desvenlafaxine Fumarate Tablet, Extended Release (50 mg and 100 mg). She concluded in her 1 August 2013 review that the Microbial Limits specification for the Desvenlafaxine Fumarate Tablet, Extended Release is acceptable from a Product Quality Microbiology perspective and that this NDA is recommended for approval from the standpoint of product quality microbiology.

4.3 Preclinical Pharmacology/Toxicology

Dr. Shiny Mathew (Pharmacology/Toxicology) concluded in her 12/17/2013 review that there are no Pharmacology/Toxicology issues that would prevent approval of this NDA.

Sun has not conducted nor plans to conduct any nonclinical study. In the written response to the Pre-IND briefing package, the Agency agreed that no nonclinical study would be required for the NDA of Desvenlafaxine ER Tablets, unless impurities / degradants or novel excipients in the drug substance or product required additional nonclinical assessment. The Applicant states that no impurity / degradant is above the ICH qualification threshold and no novel excipient is used. In addition, the Applicant states that the amount of fumarate to be delivered in the highest strength tablet (144.07 mg fumarate per tablet) does not exceed the amounts in other approved drug products. The Applicant notes that initial product development of Pristiq® was with the fumarate monohydrate salt. Wyeth performed a number of acute and subchronic toxicity studies in rodents and dogs using the desvenlafaxine fumarate monohydrate. The Applicant states that results from these studies served as “bridge” to demonstrate comparable toxicity profiles between the fumarate salt and the succinate salt used in Pristiq®.

The Applicant provides a table that presents an overview of these Wyeth studies:

Table 2: Toxicology Studies with Desvenlafaxine Fumarate (NDA 21992)
Overview of Toxicology Studies with Desvenlafaxine Fumarate
(Based on Pharmacology Review for NDA 21-992)

Study Report No.	Species/Strain/Sex	Method of Administration	Duration	Doses (mg/kg or mg/kg/day)
<i>Single-dose toxicity</i>				
GTR-15786	Guinea pigs	Intravenous	Single	Up to 10
GTR-15230	Male and female CD Charles River rats	Oral gavage	Single	0, 2500, 3000, 3500, 4000
GTR-15229	Male and female CD Charles River mice	Oral gavage	Single	0, 1600 (F only), 1800, 1900 (F only), 2100, 2400, 3000
GTR-15170	Male and female CD-1 mice	Oral gavage	Single	0, 200, 300, 400, 500, 800, 1100, 1500, 2000, 2500
<i>Repeated-dose toxicity</i>				
GTR-15148	Male and female Beagle dogs	Oral capsule	1 week	0, 50, 150, 250
GTR-16363	Male and female Beagle dogs	Oral capsule	1 month	0, 15, 75, 175

Source: Nonclinical Overview, p.3

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The exact mechanism of the antidepressant action of desvenlafaxine is unknown, but is thought to be related to the potentiation of serotonin and norepinephrine in the central nervous system, through inhibition of their reuptake.

4.4.2 Pharmacodynamics

Sun has not conducted any pharmacology studies with the proposed product. The information in the Pristiq® label will serve as the basis for Sun's label:
Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic/cholinergic, H1- histaminergic, or α1-adrenergic receptors in vitro. Desvenlafaxine also lacked monoamine oxidase (MAO) inhibitory activity.

4.4.3 Pharmacokinetics

See Section 6 for a brief review of the pivotal bioequivalence studies.

Summary of Office of Clinical Pharmacology's Review

Dr. Kofi Kumi (OCP) supports a recommendation for the approval of Desvenlafaxine fumarate ER (SUN Pharma) at the same dosing recommendation approved for Pristiq ER for the treatment of major depressive disorder (MDD). His 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.

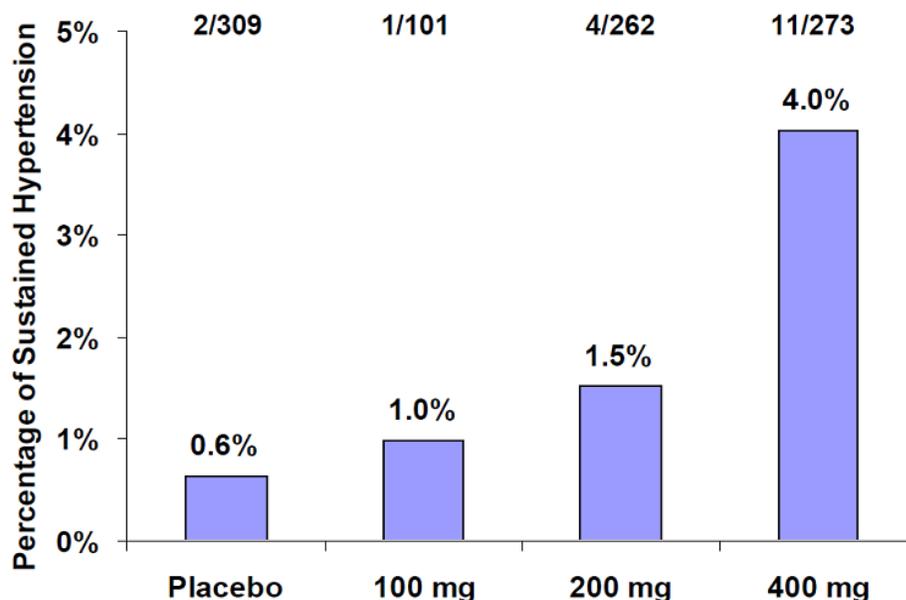
In his review, Dr. Kumi discusses the risk of sustained hypertension as it relates to the increase in C_{max} and AUC when Desvenlafaxine fumarate ER is given with food. The following is an excerpt from his review:

Sustained hypertension

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 37% increase in exposure after administration 50 mg and 100 mg Desvenlafaxine fumarate ER (SUN) with food would approximate dosing patients with about 70 and 140 mg of Desvenlafaxine fumarate ER, respectively. Since sustained hypertension occurs in a dose dependent manner, it is predicted that the percentage of patients with sustained hypertension after administration with 50 mg and 100 mg Desvenlafaxine fumarate ER would be less than 1% and 1.5%, respectively. The label recommends that blood pressure should be monitored on a regular basis when patients are on Desvenlafaxine ER tablets. And 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.

Dr. Kumi excerpted this figure from the original NDA (21992) review of the reference listed drug, Pristiq, to illustrate the dose dependency of the sustained hypertension:

Figure 2: Dose Dependent Sustained Hypertension (OCP analysis)



Source: OCP review of Pristiq (NDA 21992)

Reviewer Comment:

I agree with Dr. Kumi's conclusions and recommendations.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Sun has conducted a total of eight bioequivalence studies in a total of 194 healthy male subjects. Of these, five were pilot studies of development formulations, one was a pilot study of the final formulation, and two were pivotal bioequivalence studies. Multimedia *in vitro* dissolution testing and *in vitro* dissolution in alcoholic media, consistent with the Agency's recommendations, have also been conducted.

The Applicant's table below details the specifics of the three studies conducted with the final formulation.

**Table 3: NDA 205583 Bioequivalence Studies Conducted with Final Formulation
 Overview of Fed and Fasting Bioequivalence Studies
 of Desvenlafaxine ER Tablets, 50 mg and 100 mg**

Study Number (dates of conduct)	No. (completed) Age (yrs) BMI (kg/m ²)	Design	Product Tested	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

Source: Clinical Overview, p.7

5.2 Review Strategy

The safety data from the clinical study reports of Study 170 and Study 171 were reviewed in detail. The Integrated Summary of Safety and Clinical Summary were also reviewed in detail. Raw safety sets were reviewed in JMP and compared to the safety detailed in the clinical study reports. The proposed labeling was reviewed with the team. Finally, the reviews from the other members of the team were reviewed and summarized for this review.

5.3 Discussion of Individual Studies/Clinical Trials

The designs and results of the two pivotal bioequivalence studies (Study 170 and Study 171) will be summarized in Section 6 of this review. Safety data (as summarized in the ISS) from the eight bioequivalence studies conducted with development and final formulations will be detailed in Section 7 of this review. Safety data specific to the two pivotal bioequivalence studies (Study 170 and Study 171) will also be summarized in Section 7.

6 Review of Bioequivalence Studies

Bioequivalence Summary

The designs of the two pivotal bioequivalence studies (Study 170 and Study 171) were similar. Both were randomized, crossover, single dose studies. Study 170 was a 3-way crossover and studied the 100 mg dose of the test (Desvenlafaxine ER Tablets) and the RLD product (Pristiq® 100 mg). Study 170 included a food effect arm for the test product (Desvenlafaxine ER Tablets 100 mg). Study 171 was a 2-way crossover study and studied the 50 mg dose of the test and the RLD product (Pristiq® 50 mg) under fasting conditions.

In both Studies 170 and 171, subjects were dosed with either the test or reference product in a randomly assigned sequence, following a fast of at least 10 hours prior to dosing. Each dose was administered with 240 mL water and fasting continued for 4 hours post-dose. To study the effect of food, one arm in Study 170 included dosing of the test product with a high-fat meal. All dosing periods were separated by a washout period of 7 days. Blood samples were collected frequently up to 72 hours post-dose.

These 2 pivotal bioequivalence studies completed with the proposed formulation of Desvenlafaxine ER Tablets, 50 mg and 100 mg, demonstrate that Sun's product is bioequivalent to the approved RLD Pristiq® when administered in the same dose in the fasting state. The mean plasma concentration profiles from Study 170 and Study 171 demonstrate that the 90% confidence intervals (CI) of ratios of least squares means for C_{max} and AUC are within the bioequivalence boundaries of 80-125%.

6.1 Study 170

Title: "Randomized, 3-Way Crossover, Single Dose, Food Effect and Fasting Bioequivalence Study of Desvenlafaxine 100 mg ER Tablet"

6.1.1 Methods

Objectives:

- To assess the bioequivalence of Desvenlafaxine 100 mg Extended Release Tablets of Sun Pharmaceutical Industries Limited, India (test product) and Pristiq® 100 mg Extended Release Tablets (reference product) under fasting conditions
- To evaluate the effect of food on PK parameters of the test product when administered under fasting and fed condition
- To monitor the safety of the subjects participating in the study

Study Design

The clinical study center for Study 170 was the Clinical Pharmacology Unit of Sun Pharmaceutical Industries Ltd in Vadodara, India.

Study 170 was a randomized, open label, three treatment, three periods, six sequence, single dose, bioequivalence study of Desvenlafaxine 100 mg ER Tablets and Pristiq® 100mg ER under fasting conditions and a study to evaluate the effect of food on pharmacokinetic parameters of Desvenlafaxine 100 mg Extended Release Tablets when administered under fasting and fed condition.

A single oral dose of one tablet of either the test product (under fasting or fed condition) or reference product (under fasting condition) was administered, in each study period. Study periods were separated by a washout period of 7 days.

The three treatments were:

- Desvenlafaxine 100 mg ER Tablets under fasting condition (Treatment A)
- Desvenlafaxine 100 mg ER Tablets under fed condition (Treatment B)
- Pristiq® 100 mg ER Tablets under fasting condition (Treatment C)

Subjects

Key Inclusion Criteria

- Healthy males, 18 to 45 years of age
- Weight \geq 50 kg
- BMI 18.5 to 25 kg/m²
- No evidence of underlying disease on screening medical history, physical exam, laboratory, ECG, and chest x-ray

Key Exclusion Criteria

- History or presence of cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, musculoskeletal, neurological or psychiatric disease
- Narrow angle Glaucoma
- Use of MAO inhibitors 14 days prior to start of study or use of enzyme-modifying drugs (e.g., Phenytoin, Carbamazepine, Barbiturates, Griseofulvin) in the previous 30 days before start of study
- Smoking (\geq 10 cigarettes/day) or consumption of tobacco products (\geq 4 chews/day)
- Systolic blood pressure $<$ 90 or $>$ 140; diastolic blood pressure $<$ 60 or $>$ 90; pulse rate $<$ 60/minute or $>$ 100/minute

Blood Sampling Points

Blood samples for PK endpoints were collected before dosing and at 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 11.00, 12.00, 13.00, 14.00, 16.00, 24.00, 36.00, 48.00, 60.00 and 72.00 hours post-dose.

Criteria for Evaluation

- Primary Pharmacokinetic Parameters were AUC_{0-t} , AUC_{0-inf} , and C_{max} .
- Secondary Pharmacokinetic Parameters were % AUC Extrapolation, AUC_{0-t} / AUC_{0-inf} , T_{max} , K_{el} , and $T_{1/2}$.
- Safety assessments included adverse events, vital signs, ECGs, and standard laboratory evaluations.

Statistical Methods

Standards:

To claim bioequivalence, the 90% geometric confidence interval of relative geometric means C_{max} , AUC_{0-t} and AUC_{0-inf} of the test product (fasting) vs. reference product (fasting) should be between 80.00% and 125.00% for Ln-transformed data.

To assess food effect, the ratio of means and 90% confidence interval for Ln-transformed data shall be calculated between test product administered under fed (treatment B) vs. fasting (treatment A) condition.

6.1.2 Demographics

The subjects were 36 Indian (Asian) males.

Table 4: Study 170 Demographics

Parameter	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m²)
Mean	33.5	165.2	60.1	22.01
SD (±)	6.98	4.86	6.01	1.73
Range (min)	20	155	50.7	19
Range (max)	44	174	71.5	25
CV%	20.8	2.9	10	7.9

Source: Study 170 Demographic Data, p.2

6.1.3 Subject Disposition

Table 5: Study 170 Subject Disposition

Parameter	N
Randomized	36
Reported	43
Enrolled	36 + 4 (extra housed)
Discontinued	4
Completed	32
Data set for safety analysis	36
Data set for PK and statistical analysis (A vs C)	33
Data set for PK and statistical analysis (B vs A)	33

Source: Synopsis, p.2

Protocol Deviations

There was no protocol deviations observed during the conduct of study and reporting of results. There was one deviation in the blood sampling schedule for one subject during Period I:

Table 6: Study 170 Blood Sampling Schedule Deviation

Subject Number	Time Point (hour)	Time of Collection (HH:MM)		Deviation (Minutes)
		Scheduled	Actual	
17	60.00	08:32 pm	09:45 pm	+73

Source: Study 170 Protocol Deviations, p. 3

6.1.4 Analysis of the Primary Pharmacokinetic Endpoint

Bioequivalence

Study 170, using the proposed formulation to be marketed of Desvenlafaxine ER Tablets 100 mg, demonstrated that Sun's product is bioequivalent to the approved RLD Pristiq® when administered in the same dose in the fasting state. The mean plasma concentration profiles from Study 170 demonstrate that the 90% confidence intervals (CI) of ratios of least squares means for C_{max} and AUC are within the bioequivalence boundaries of 80-125%.

The table below gives a summary of the results of the PK parameters:

Table 7: Study 170 Summary of Results of PK Parameters

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: Synopsis, p.5

The Ln-transformed data are displayed in the table below. The ratios of the least-square means (and 90% geometric confidence intervals) of the Test to Reference product (A/C) for Desvenlafaxine were 89.32 (80.96 to 98.55) % for AUC_{0-t}, 89.39 (80.98 to 98.67) % for AUC_{0-inf} and 89.27 (83.66 to 95.25) % for C_{max} for the Ln-transformed data. These ratios and confidence intervals were within the limits of 80.00% to 125.00%. Therefore, bioequivalence between the Test product and Reference product can be declared when administered under fasting condition.

Table 8: Study 170 Summary of Statistical Analysis Desvenlafaxine Ln-Transformed Data

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

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

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

Source: Synopsis, p.5

Food Effect

A food effect was demonstrated for the test product (Desvenlafaxine 100 mg ER tablet). For the Ln-transformed data, the ratios of least-square means (and 90% geometric confidence intervals) between the test product administered under fed condition (treatment B) and the test product administered under fasting condition (treatment A) were not between 80% and 125% for AUC_{0-t}, AUC_{0-inf}, and C_{max}.

When Desvenlafaxine 100 mg ER tablet was given with a high-calorie, high-fat breakfast, there was an increase in absorption. AUC_{0-t} and AUC_{0-inf} values were approximately 29% higher in the fed state. C_{max} was about 37% higher and T_{max} occurred 2.50 hours later. The RLD Pristiq® also demonstrates a food effect, although to a lesser extent. Section 12.3 Pharmacokinetics of the current Pristiq® label describes the following food effect:

“A food-effect study involving administration of PRISTIQ to healthy subjects under fasting and fed conditions (high-fat meal, 800 to 1000 calories) indicated that desvenlafaxine C_{max} was increased about 16% in the fed state, while the AUCs were similar. This difference is not expected to be clinically significant; therefore, PRISTIQ can be taken without regard to meals [see *Dosage and Administration (2.1)*].”

The data demonstrating the food effect for the test product are detailed in the tables below:

Table 9: Study 170 Summary of Results of Desvenlafaxine PK Parameters, Food Effect

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, Synopsis p.6

Table 10: Study 170 Summary of Statistical Analysis Desvenlafaxine Ln-Transformed Data, Food Effect

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 B	Treatment A	Treatment B	Treatment A				
AUC _{0-t}	8.85	8.59	6955.14	5378.35	129.32	115.90 to 144.29	26.15	0.0004
AUC _{0-inf}	8.86	8.60	7039.71	5457.77	128.98	115.62 to 143.89	26.10	0.0005
C _{max}	5.81	5.50	332.93	243.79	136.57	127.65 to 146.11	15.94	< 0.0001

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

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

Source, Synopsis p. 6

Reviewer's Comment:

It should be noted that although AUC_{0-t} and AUC_{0-inf} values were ~ 29% higher in the fed state and C_{max} was ~ 37% higher, the majority of treatment-emergent adverse events in the 8 bioequivalence studies occurred when desvenlafaxine was dosed in the fasting state (see Section 7.5.2 of this review).

6.1.6 Other Endpoints

**Table 11: Study 170 Desvenlafaxine Mean Plasma Concentration-Time Profile (Treatment A vs C)
 Desvenlafaxine Mean Plasma Concentration – Time Profile (Treatment ‘A’ vs. ‘C’)**

Summary of plasma Desvenlafaxine concentrations at each sampling time point comparing Desvenlafaxine 100mg Extended Release Tablets (Treatment A) of Sun Pharmaceutical Industries Limited, India, and Pristiq® (Desvenlafaxine) 100mg Extended Release Tablets (Treatment C) of Wyeth Pharmaceuticals Inc., Philadelphia, PA 19101, in 33 healthy male subjects, under fasting condition.

Least Square Means (ng/mL)

Collection Time (hr.)	Treatment A LSM	Treatment C LSM	Significance [#]	p Value
0.00	0.0000	0.0000	None	1.0000
1.00	35.3925	50.3887	< 0.05	0.0000
2.00	107.9081	142.4991	< 0.05	0.0000
3.00	163.8770	208.5811	< 0.05	0.0000
4.00	191.8958	239.9443	< 0.05	0.0000
5.00	218.6556	261.4433	< 0.05	0.0000
6.00	225.4512	260.7480	< 0.05	0.0006
7.00	233.4335	259.9880	< 0.05	0.0109
8.00	229.4982	250.5106	None	0.0570
9.00	220.7976	237.4843	None	0.1230
10.00	213.4588	232.4539	None	0.0741
11.00	203.1623	220.9228	None	0.0559
12.00	200.0080	211.4851	None	0.2550
13.00	195.8746	205.0177	None	0.3286
14.00	191.1186	195.0348	None	0.6594
16.00	185.3563	181.1163	None	0.6275
24.00	126.9475	124.5978	None	0.7715
36.00	56.1022	59.4889	None	0.4841
48.00	26.5876	27.0046	None	0.8792
60.00	11.5452	11.9055	None	0.7726
72.00	5.4388	5.5804	None	0.8245

[#]Results of the statistical evaluation by ANOVA ($\alpha=0.05$) for the hypothesis of equal treatment effects. None indicate that no statistical significant difference was detected between treatment means ($P >0.05$) at the sampling time evaluated.

Source: Synopsis, p. 7

6.1.7 Subpopulations

The Sun-sponsored pivotal bioequivalence studies were performed in healthy adult Asian (Indian) males ranging in age from 19 to 49 years. Therefore, no subpopulations were studied.

6.2 Study 171

Title: "Randomized, 2-Way Crossover, Single Dose, Fasting Bioequivalence Study of Desvenlafaxine 50 mg ER Tablet"

6.2.1 Methods

Objectives:

- To assess the bioequivalence of Desvenlafaxine 50 mg Extended Release Tablets of Sun Pharmaceutical Industries Limited, India (test product) and Pristiq® 50 mg Extended Release Tablets (reference product) under fasting conditions
- To monitor the safety of the subjects participating in the study

Study Design

Study 171 was conducted at the clinical study center for Sun Pharmaceutical Industries Ltd in Vadodara, India.

Study 171 was a randomized, open label, two treatment, two periods, two sequence, single dose, crossover, bioequivalence study of Sun Pharmaceutical's Desvenlafaxine 50 mg ER Tablets (test product) and Wyeth's Pristiq® 50mg ER (reference product) under fasting conditions.

A single oral dose of either the test product (under fasting condition) or reference product (under fasting condition) was administered, in each study period. Study periods were separated by a washout period of 7 days.

The two treatments were:

- Desvenlafaxine 50 mg ER Tablets under fasting condition (Treatment A)
- Pristiq® 50 mg ER Tablets under fasting condition (Treatment B)

Subjects

Subjects were 50 healthy adult male subjects. The inclusion and exclusion criteria were identical to Study 170.

Blood Sampling Points

Blood samples for PK endpoints were collected before dosing and at 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 11.00, 12.00, 16.00, 24.00, 36.00, 48.00, 60.00 and 72.00 hours post-dose.

Criteria for Evaluation

- Primary Pharmacokinetic Parameters were AUC_{0-t} , AUC_{0-inf} , and C_{max} .
- Secondary Pharmacokinetic Parameters were % AUC Extrapolation, AUC_{0-t} / AUC_{0-inf} , T_{max} , K_{el} , and $T_{1/2}$.
- Safety assessments included adverse events, vital signs, ECGs, and standard laboratory evaluations.

Statistical Methods

Standards:

Criteria for bioequivalence: The 90% geometric confidence interval of relative geometric means C_{max} , AUC_{0-t} and AUC_{0-inf} of the test product and reference product should be between 80.00% and 125.00% for Ln-transformed data.

6.2.2 Demographics

The subjects were 50 Indian (Asian) males.

Table 12 Study 171 Demographics

Parameter	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)
Mean	32.5	167.1	61.0	21.79
SD (±)	6.27	6.13	7.99	2.03
Range (min)	21	158	50.45	18.6
Range (max)	44	181	81.45	25
CV%	19.3	3.7	13.1	9.3

Source: Study 171 Demographic Data, p.3

6.2.3 Subject Disposition

Table 13: Study 171 Subject Disposition

Parameter	N
Randomized	50
Reported	58
Enrolled	50 + 6 (extra housed)
Discontinued	3
Completed	47
Data set for safety analysis	50
Data set for PK and statistical analysis	47

Source: Synopsis, p.2

Protocol Deviations

There was no protocol deviations observed during the conduct of study and reporting of results. There were no deviations noted in the blood sampling schedule.

6.2.4 Analysis of the Primary Pharmacokinetic Endpoint

Table 14: Study 171 Summary of Results Desvenlafaxine PK Parameters

SUMMARY OF RESULTS								
DESVENLAFAXINE (N = 47)								
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: Synopsis, p. 5

The Ln-transformed data are displayed in the table below. The ratios of the least-square means (and 90% geometric confidence intervals) of the Test to Reference product (A/B) for Desvenlafaxine were 90.26 (81.62 to 99.82) % for AUC_{0-t}, 90.15 (81.58 to 99.61) % for AUC_{0-inf} and 91.86 (87.71 to 96.20) % for C_{max} for the Ln-transformed data. These ratios and confidence intervals were within the limits of 80.00% to 125.00%. Therefore, bioequivalence between the Test product and Reference product can be declared when administered under fasting condition.

Table 15: Study 171 Summary of Statistical Analysis Desvenlafaxine Ln-Transformed Data

SUMMARY OF STATISTICAL ANALYSIS DESVENLAFAXINE (N = 47)								
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	Reference				
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

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

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

Source: Synopsis, p.5

6.2.6 Other Endpoints

Table 16: Desvenlafaxine Mean Plasma Concentration-Time Profile
 Desvenlafaxine Mean Plasma Concentration – Time Profile

Summary of plasma Desvenlafaxine concentrations at each sampling time point comparing Desvenlafaxine 50 mg Extended Release Tablets (Test) of Sun Pharmaceutical Industries Limited, India, and Pristiq® (Desvenlafaxine) 50 mg Extended Release Tablets (Reference) of Wyeth Pharmaceuticals Inc., Philadelphia, PA 19101, in 47 healthy adult human subjects, under fasting conditions.

Least Square Means (ng/mL)

Collection Time (hr.)	TestLSM	RefLSM	Significance [#]	p Value
0.00	0.0000	0.0000	None	1.0000
1.00	23.5212	29.7076	< 0.05	0.0000
2.00	59.0701	71.3778	< 0.05	0.0000
3.00	84.8320	102.6837	< 0.05	0.0000
4.00	98.2714	116.7477	< 0.05	0.0000
5.00	105.9328	120.6429	< 0.05	0.0000
6.00	105.5486	118.4170	< 0.05	0.0004
7.00	106.1789	116.1057	< 0.05	0.0073
8.00	105.5395	111.4776	None	0.1352
9.00	102.3467	108.1274	None	0.1951
10.00	98.3385	103.2933	None	0.2896
11.00	93.2308	96.2231	None	0.5103
12.00	89.7637	93.3123	None	0.4473
16.00	79.0690	78.5912	None	0.9256
24.00	55.7543	60.4515	None	0.3462
36.00	23.5720	27.5938	None	0.1559
48.00	10.7695	13.1482	None	0.1656
60.00	4.2886	5.7014	None	0.1337
72.00	1.5422	2.4679	None	0.1058

[#]Results of the statistical evaluation by ANOVA ($\alpha=0.05$) for the hypothesis of equal treatment effects. None indicate that no statistical significant difference was detected between treatment means ($P > 0.05$) at the sampling time evaluated.

Source: Synopsis, p.6

6.2.7 Subpopulations

The Sun-sponsored pivotal bioequivalence studies were performed in healthy adult Asian (Indian) males ranging in age from 19 to 49 years. Therefore, no subpopulations were studied.

7 Review of Safety

Safety Summary²

During the development program for desvenlafaxine fumarate, Sun sponsored eight bioequivalence studies, of which three used the formulation proposed for marketing and five used earlier formulations. In total, 194 healthy adult Asian male volunteers between the ages of 19 to 49 years were exposed to at least one dose of Sun's Desvenlafaxine Extended Release Tablets or Pristiq®, with 106 subjects receiving Sun's proposed final formulation. Based on the results of bioequivalence testing, the various formulations are considered sufficiently similar that safety results can be pooled.

Overall, there were few adverse events reported in the eight single-dose crossover bioequivalence studies sponsored by Sun. Adverse events were consistent with the safety profile of desvenlafaxine, based on the approved labeling (February 2013). There were no new or unexpected safety findings, compared to the known safety profile of desvenlafaxine succinate.

Across the 8 bioequivalence studies, there were no deaths. One subject who received the test product (Desvenlafaxine ER 100 mg fasting) experienced an SAE of a hospitalization for acute gastroenteritis. However, this SAE occurred ~ 3 days after the test product was administered.

Diarrhea was the most common reason for discontinuation for both the test product (3.2%) and the RLD (3.2%). Across the 8 studies, 24 subjects (12.4%) reported at least one adverse event not related to a laboratory test parameter. All but one of these subjects received a desvenlafaxine dose of 100 mg. Adverse events were primarily gastrointestinal, with diarrhea being the most common event (16 subjects or 8.2%), regardless of study treatment. Other gastrointestinal events that occurred in more than 1 subject were nausea (3 subjects or 1.5%) and vomiting (2 subjects or 1.0%). Dizziness, headache, and somnolence each occurred in 2 subjects (1.0%).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Sun has sponsored eight single-dose crossover bioequivalence studies. Three studies used the formulation proposed for marketing and five used earlier formulations. Of the

² Given the relatively brief duration of the bioequivalence studies, and the subject samples for these studies (healthy volunteers), the conducted studies are not capable of producing meaningful new safety data that could be extrapolated to the clinical use of desvenlafaxine products. However, there is extensive safety experience with Pristiq and its parent compound, Effexor (venlafaxine).

three studies that used the formulation proposed for marketing, one was a pilot study (Study 382) and two were the pivotal studies (Study 170 and Study 171).

The Applicant's integrated summary of safety (ISS) is based on the eight single-dose crossover bioequivalence studies. In this section of the review, I will summarize the findings detailed in the ISS and also summarize the safety findings detailed in the individual study reports of the two pivotal bioequivalence studies conducted with the proposed formulation (Study 170 and Study 171).

The Applicant's ISS is based on the safety data from the eight bioequivalence studies detailed in the Applicant's table below:

Table 17: Overview of Sources of Safety Data for ISS
Overview of Sources of Safety Data for Desvenlafaxine Fumarate

Study No.	No. Randomized (Exposed)	Dates of Conduct (Location)	Demographics Mean (range)	Overview of Design (Dose)
Single-Dose Bioequivalence Studies in Healthy Adult Volunteers				
Studies of Proposed Formulation				
PKD_12_170	36 (36) ¹	28 May 2012 – 16 June 2012 (India)	36 M / 36 Asian Age (years): 33.5 (20-44) BMI (kg/m ²): 22.0 (19.0-25.0)	Randomized, 3-way crossover, single-dose, fasted BE and food effect study (100 mg)
PKD_12_171	50 (50) ¹	04 August 2012 – 16 August 2012 (India)	50 M / 50 Asian Age (years): 32.5 (21-44) BMI (kg/m ²): 21.8 (18.6-25.0)	Randomized, 2-way crossover, single-dose, fasted BE study (50 mg)
PKD_11_382	16 (16) ¹	19 Nov 2011 – 30 Nov 2011 (India)	16 M / 16 Asian Age (years): 30.1 (23-39) BMI (kg/m ²): 21.6 (18.6-24.3)	Randomized, 2-way crossover, single-dose, fasted BE study (100 mg)
Studies of Earlier Formulations				
PKD_11_033	20 (20) ¹	2 Feb 2011 – 14 Feb 2011 (India)	20 M / 20 Asian Age (years): 30.9 (19-43) BMI (kg/m ²): 21.5 (18.7-25.0)	Randomized, 2-way crossover, single-dose, fasted BE study (100 mg) ²
PKD_11_034	20 (20) ¹	2 Feb 2011 – 14 Feb 2011 (India)	20 M / 20 Asian Age (years): 33.1 (20-49) BMI (kg/m ²): 21.7 (18.7-25.0)	Randomized, 2-way crossover, single-dose, fed BE study (100 mg) ²
PKD_11_271	20 (20)	21 June 2011 – 3 July 2011 (India)	20 M / 20 Asian Age (years): 31.9 (24-45) BMI (kg/m ²): 21.5 (19.7-25.0)	Randomized, 2-way crossover, single-dose, fasted BE study (100 mg) ³
PKD_11_272	20 (20) ¹	21 June 2011 – 3 July 2011 (India)	20 M / 20 Asian Age (years): 33.1 (24-44) BMI (kg/m ²): 22.3 (18.6-25.0)	Randomized, 2-way crossover, single-dose, fed BE study (100 mg) ³
PKD_11_348	12 (12) ¹	11 Oct 2011 – 22 Oct 2011 (India)	12 M / 12 Asian Age (years): 32.8 (21-44) BMI (kg/m ²): 21.6 (19.3-23.9)	Randomized, 2-way crossover, single-dose, fasted BE study (50 mg) ³
TOTAL	194 (194)	--	194 M / 194 Asian Age 19-49 years BMI 18.6-25.0 kg/m²	--

BE = bioequivalence; M = male

¹ Additional subjects were enrolled and housed as extra subjects until dosing commenced in case of any pre-dose drop outs; they were not dosed.

² C_{max} and 36 to 46% higher than reference product; AUC 6 to 26% higher.

³ Met criteria for bioequivalence

Source: ISS, p.5

7.1.2 Categorization of Adverse Events

Adverse events are categorized only by the “investigator’s term” and the preferred term. No reference to a specific MedDRA coding dictionary is given.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data for the ISS are pooled across the eight single-dose crossover bioequivalence studies. The designs of these eight studies were sufficiently similar to justify this pooling.

7.2 Adequacy of Safety Assessments

All tests reasonably applicable were conducted to assess the safety of the test and RLD products. Safety was assessed by monitoring adverse events, clinical laboratory testing, vital signs, and electrocardiograms (ECGs). Adverse events were monitored throughout the study.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In this 505(b)(2) application, the Applicant is primarily relying on the safety data from the studies conducted for the approval of the RLD. The cumulative worldwide marketing exposure to Desvenlafaxine Succinate Sustained Release (DVS SR) from 12 May 2008 (date of first marketing) through 28 February 2013 is estimated to be 1,945,464 patient-years.³

In the eight bioequivalence studies, 194 healthy adult Asian male volunteers between the ages of 19 to 49 years were exposed to at least one dose of Sun's Desvenlafaxine Extended Release Tablets or Pristiq®. The 100 mg dose was administered to 132 subjects and the 50 mg dose was administered to 62 subjects in these eight bioequivalence studies (see Table 17 for details). Sun's proposed final formulation was administered to 106 subjects.

7.2.2 Explorations for Dose Response

The Applicant notes that most of the adverse events from the pooled bioequivalence studies occurred following a 100 mg dose of desvenlafaxine in the fasted state. This is consistent with the Pristiq USPI that states that doses higher than 50 mg are associated with a greater incidence of adverse events.

7.2.4 Routine Clinical Testing

Clinical laboratory testing included hematology, biochemistry, and urinalysis parameters. Laboratory assessments were performed at Screening and/or check in to

³ From Pristiq DSUR (3/1/12-2/28/13), p.3

Period 1 and at the check-out from the last dosing period (48 hours after the final of two or three single doses).

ECGs were performed at Screening and for each treatment period at check in, between 6 to 8 hours post dose, and at check-out (48 hours after final dose).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Applicant adequately attempted to assess all potential adverse events that might be associated with this drug class.

7.3 Major Safety Results

There were no unexpected safety concerns. Overall, adverse events occurring in the eight Sun-sponsored pharmacokinetic studies were consistent with the known safety and tolerability profile for Pristiq.

7.3.1 Deaths

There were no deaths.

7.3.2 Nonfatal Serious Adverse Events

There were two SAEs in the pooled eight bioequivalence studies. Only one subject who received the test formulation experienced an SAE (Subject 34 in Study 170). The other SAE (convulsion) was experienced by a subject who received Pristiq 100 mg (fasting) in a non-pivotal study. The narrative for the subject who experienced the SAE in Study 170 is described below.

Study 170

One subject (Subject number 34) experienced an SAE of a hospitalization for acute gastroenteritis with dehydration in period II of study. It should be noted that the subject was administered the test product (100 mg fasting) on 6/6/2012 at 8:30 am. The onset of the diarrhea was ~ 3 days later. The following is the narrative for this subject:

Subject 34 had complaints of loose watery diarrhea approximately 10 times since 02:30 am on (b) (6). Diarrhea was associated with severe epigastric pain and nausea. Subject had normal vital sign measurements with 98.2°F temperature, 92/minute pulse rate and 100/68 mm of Hg blood pressure. The Subject was dropped from the study and referred to (b) (6) for treatment and further management on (b) (6). During hospitalization subject's stay was uneventful and was diagnosed as Acute Gastroenteritis with Dehydration and treated for the same. Subject had no complaints since approximately 05:00 am on (b) (6) and had normal vital sign measurements with 98.0°F temperature, 80/minute pulse rate and 108/70 mm of Hg

blood pressure. Adverse event was considered resolved on [REDACTED] (b) (6) and patient was discharged from the hospital on the same day. He was advised to complete the medication as per instruction given on discharge.

The investigator judged the reported adverse event (i.e. Epigastric pain) was unrelated to treatment administered and remaining adverse events (diarrhea and nausea) were possibly related with test treatment.

Study 171

There were no SAEs reported.

7.3.3 Dropouts and/or Discontinuations

ISS

For the eight pooled bioequivalence studies, 16 subjects (8.2%) were discontinued from study treatment for adverse events, all but one following dosing in the fasted state. The number of subjects who discontinued was similar for the test product and the RLD. Diarrhea was the most common reason (12 subjects or 6.2%) followed by headache (2 subjects or 1.0%). Adverse events resulting in discontinuation by test product versus RLD are detailed in the Applicant's table below:

Table 18: ISS Adverse Events Resulting in Discontinuation

Preferred term	N (%)		Study No.	Subject No.
	Desvenlafaxine ER Tablets (N=186)	Desvenlafaxine Succinate ER Tablets (Pristiq®) (N=188)		
Total no. of subjects with ≥1 AE resulting in discontinuation	7 (3.8%)	9 (4.8%)	--	--
Convulsion	0	1 (<1%) ²	PKD_11_033	18
Diarrhea	6 (3.2%) ¹	6 (3.2%)	PKD_12_170	03, 13, 15, 34
			PKD_12_171	33
			PKD_11_033	11
			PKD_11_271	05, 06, 10, 13, 16
			PKD_11_382	06
Dyspepsia	1 (<1%) ¹	0	PKD_12_170	34
Foaming at mouth	0	1 (<1%) ²	PKD_11_033	18
Headache	0	2 (1.1%)	PKD_11_033	11
			PKD_11_271	13
Hyperhidrosis	0	1 (<1%) ²	PKD_11_033	18
Injection site pain ³	0	1 (<1%)	PKD_12_171	08
Nausea	1 (<1%) ¹	0	PKD_12_170	34
Swelling face	0	1 (<1%)	PKD_11_272	10
Vomiting	1 (<1%)	0	PKD_12_171	04

Source: Study PKD_12_170 and Study PKD_12_171, Table 16.2.7-1; Study PKD_11_033, Study PKD_11_034, Study PKD_11_271, Study PKD_11_272, Study PKD_11_348, and Study PKD_11_382, Appendix 11.2

¹ Met criteria for an SAE in 1 subject (Subject 34 in Study PKD_12_170)

² Met criteria for an SAE in 1 subject (Subject 18 in Study PKD_11_033)

³ Considered to be a coding error; the correct preferred term is "muscular pain".

Source: ISS, p.11

Subjects who discontinued in the pivotal studies are detailed in the tables below:
Study 170

Table 19: Study 170 Discontinuations

Subject Number	Reason For Dropout/replacement
03	Due to adverse event and required concomitant medication in period I
13	Due to adverse event and required concomitant medication in period I
15	Due to adverse event and required concomitant medication in period I
26*	The subject withdrew himself without any reason, voluntarily before dosing in period I
34	Due to serious adverse event in period II

*Subject number 26 withdrew himself without any reason, voluntarily before dosing in period I and was replaced with subject number E-26.

Source: Study 170 Discontinued Subjects, p. 2

Study 171

Table 20: Study 171 Discontinuations

Subject Number	Reason For Dropout/replacement
04	Due to adverse event and required concomitant medication in period I.
08	Due to adverse event and required concomitant medication in period I
33	Due to adverse event and required concomitant medication in period II
45*	Withdrew himself without any reason, voluntarily before dosing in period I.

*Subject number 45 withdrew himself without any reason, voluntarily before dosing in period I and was replaced with extra subject (Subject number E-45).

Source: Study 171 Discontinued Subjects, p. 2

7.3.4 Significant Adverse Events

ISS

Across the 8 bioequivalence studies, 24 subjects (12.4%) reported at least one adverse event not related to a laboratory test parameter. All but one of these subjects received a desvenlafaxine dose of 100 mg. Adverse events were primarily gastrointestinal. Diarrhea was the most common adverse event (16 subjects or 8.2%), regardless of study treatment. Other gastrointestinal events that occurred in more than 1 subject were nausea (3 subjects or 1.5%) and vomiting (2 subjects or 1.0%). Dizziness, headache, and somnolence each occurred in 2 subjects (1.0%).

Table 21: ISS Adverse Events Across the 8 Bioequivalence Studies

Preferred term	N (%)	
	Desvenlafaxine ER Tablets (N=186)	Desvenlafaxine Succinate ER Tablets (Pristiq®) (N=188)
Abdominal pain	0	1 (<1%)
Chills	0	1 (<1%)
Convulsion	0	1 (<1%)
Diarrhea	9 (4.8%)	8 (4.3%)
Diarrhea haemorrhagic	0	1 (<1%)
Dizziness	1 (<1%)	1 (<1%)
Dyspepsia	1 (<1%)	0
Foaming at mouth	0	1 (<1%)
Groin pain	1 (<1%)	0
Headache	0	2 (1.1%)
Hyperhidrosis	0	1 (<1%)
Injection site pain ¹	0	1 (<1%)
Nausea	3 (1.6%)	0
Somnolence	1 (<1%)	1 (<1%)
Swelling face	0	1 (<1%)
Vomiting	2 (1.1%)	0

¹Considered to be a coding error, the correct preferred term is “muscular pain”
 Source: ISS, p.8

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The tables below provide details of the adverse events in the pivotal studies with respect to onset time, duration, intensity, and action taken.

Study 170

Table 22: Study 170 Adverse Events with Respect to Onset Time, Duration, Intensity, and Action Taken

Period I

Subject Number	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	Cause	Action Taken
		Investigators Term	Preferred Term								
03	C	Diarrhoea	Diarrhoea	30/05/12	Approx. 12:20 pm	08:04 am 30/05/12	30/05/12 03:00 pm	2	3	3	4,5
13	A	Diarrhea	Diarrhoea	30/05/12	04:30 pm	08:24 am 30/05/12	30/05/12 Approx. 05:40 pm	2	3	3	4,5
15	A	Diarrhoea	Diarrhoea	30/05/12	Approx. 03:04 pm	08:28 am 30/05/12	30/05/12 06:00 pm	2	3	3	4,5
Treatment: A = Desvenlafaxine 100 mg ER Tablets (Fasting condition) Treatment: B = Desvenlafaxine 100 mg ER Tablets (Fed condition) Treatment: C = Pristiq® (Desvenlafaxine) 100mg ER Tablets (Fasting condition)											
Intensity : 1 = Mild, 2 = Moderate, 3 = Severe											
Action Taken : 1=None, 2 = Increased Surveillance, 3 = Follow up, 4= Medication, 5 = Withdrawn, 6 = Hospitalization											
Occurrence : 1= Single Episode, 2 = Intermittent, 3 = Continuous											
Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.											

Period II

Subject Number	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	Cause	Action Taken
		Investigators Term	Preferred Term								
34	A	Diarrhoea	Diarrhoea	(b) (6)	Approx. 02:30 am	08:30 am 06/06/12	12/06/12 Approx. 05:00 am	3	3	3	5,6
		Epigastric Pain	Dyspepsia							4	
		Nausea	Nausea							3	
Treatment: A = Desvenlafaxine 100 mg ER Tablets (Fasting condition) Treatment: B = Desvenlafaxine 100 mg ER Tablets (Fed condition) Treatment: C = Pristiq® (Desvenlafaxine) 100mg ER Tablets (Fasting condition)											
Intensity : 1 = Mild, 2 = Moderate, 3 = Severe											
Action Taken : 1=None, 2 = Increased Surveillance, 3 = Follow up, 4= Medication, 5 = Withdrawn, 6 = Hospitalization											
Occurrence : 1= Single Episode, 2 = Intermittent, 3 = Continuous											
Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.											

Period III

There was no adverse event observed/reported during period III.

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Post Study

Subject Number	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	Cause	Action Taken
		Investigators Term	Preferred Term								
13	A	High Sodium	Blood sodium increased	01/06/12	11:53 am	08:24 am 30/05/12	04/06/12 04:34 pm	1	NA	4	3
15	A	High Sodium	Blood sodium increased	01/06/12	11:54 am	08:28 am 30/05/12	04/06/12 04:34 pm	1	NA	4	3
16	C (P-I) B(P-II) A(P-III)	High Triglyceride	Blood triglycerides increased	15/06/12	10:27 am	08:30 am 30/05/12 (P-I) 06/06/12 (P-II) 13/06/12 (P-III)	19/06/12 09:39 pm	1	NA	3	3
Treatment: A = Desvenlafaxine 100 mg ER Tablets (Fasting condition) Treatment: B = Desvenlafaxine 100 mg ER Tablets (Fed condition) Treatment: C = Pristiq® (Desvenlafaxine) 100mg ER Tablets (Fasting condition)											
Intensity : 1 = Mild, 2 = Moderate, 3 = Severe											
Action Taken: 1=None, 2 = Increased Surveillance, 3 = Follow up, 4= Medication, 5 = Withdrawn, 6 = Hospitalization											
Occurrence: 1= Single Episode, 2 = Intermittent, 3 = Continuous											
Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.											

Source: Study 170 Adverse Events, p. 2-4

Study 171

Table 23: Study 171 Adverse Events with Respect to Onset Time, Duration, Intensity, and Action Taken

Period I

Subject Number	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	Cause	Action Taken
		Investigators Term	Preferred Term								
04	A	Vomiting	Vomiting	06/08/12	08:10 pm	08:06 am 06/08/12	06/08/12 08:50 pm	2	1	3	2,4,5
08	B	Pain in right forearm	Musculoskeletal pain	06/08/12	02:20 pm	08:14 am 06/08/12	06/08/12 05:40 pm	3	3	4	4,5
Treatment: A = Test, B = Reference											
Intensity : 1 = Mild, 2 = Moderate, 3 = Severe											
Action Taken: 1=None, 2 = Increased Surveillance, 3 = Follow up, 4= Medication, 5 = Withdrawn, 6 = Hospitalization											
Occurrence: 1= Single Episode, 2 = Intermittent, 3 = Continuous											
Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.											

Period II

Subject Number	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	Cause	Action Taken
		Investigators Term	Preferred Term								
33	B	Diarrhea	Diarrhoea	13/08/12	Approx. 11:36 am	08:14 am 13/08/12	13/08/12 12:55 pm	2	2	2	4,5
Treatment: A = Test, B = Reference											
Intensity : 1 = Mild, 2 = Moderate, 3 = Severe											
Action Taken: 1=None, 2 = Increased Surveillance, 3 = Follow up, 4= Medication, 5 = Withdrawn, 6 = Hospitalization											
Occurrence: 1= Single Episode, 2 = Intermittent, 3 = Continuous											
Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.											

Source: Study 171 Adverse Events, p.2-3

Reviewer's Comment:

The Applicant notes that diarrhea is not listed as a common adverse event in Pristiq's current USPI. However, diarrhea was the most common adverse event associated with both the test and RLD product in Sun's pooled bioequivalence studies. In addition, the only SAE noted in the pivotal bioequivalence studies was related to severe diarrhea after administration 100 mg of the test product in a fasting state.

The frequency of the adverse event of diarrhea in subjects who were administered the test product in Sun's pivotal bioequivalence studies along with elevated serum sodium, raises a concern that perhaps this test product is associated with more diarrhea and secondary hypernatremia than the RLD product. However, review of Pristiq's 2012 Annual Report indicates that diarrhea is very common adverse event in postmarketing reports. This knowledge, along with the fairly even distribution of diarrhea in subjects receiving the test and RLD product in Sun's pooled bioequivalence studies (4.8% versus 4.3%), makes this less of a concern.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse reactions (incidence $\geq 5\%$ and twice the rate of placebo in the 50 or 100 mg dose groups) seen in the Pristiq pivotal clinical trials were nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders.

Diarrhea and nausea were the most common adverse events seen in the pooled Sun bioequivalence studies. The other adverse events seen in these bioequivalence studies are detailed in the table below:

Table 24: ISS TEAEs Overall and by Salt

Non-Laboratory Treatment-Emergent Adverse Events for Desvenlafaxine Overall and by Salt (Regardless of Dose or Dosing Condition)

Preferred term	N (%)		
	Desvenlafaxine ER Tablets (N=186)	Desvenlafaxine Succinate ER Tablets (Pristiq®) (N=188)	Overall (N = 194)
Abdominal pain	0	1 (<1%)	1 (<1%)
Chills	0	1 (<1%)	1 (<1%)
Convulsion	0	1 (<1%)	1 (<1%)
Diarrhea	9 (4.8%)	8 (4.3%)	16 (8.2%)
Diarrhea haemorrhagic	0	1 (<1%)	1 (<1%)
Dizziness	1 (<1%)	1 (<1%)	2 (1.0%)
Dyspepsia	1 (<1%)	0	1 (<1%)
Foaming at mouth	0	1 (<1%)	1 (<1%)
Groin pain	1 (<1%)	0	1 (<1%)
Headache	0	2 (1.1%)	2 (1.0%)
Hyperhidrosis	0	1 (<1%)	1 (<1%)
Injection site pain ¹	0	1 (<1%)	1 (<1%)
Nausea	3 (1.6%)	0	3 (1.5%)
Somnolence	1 (<1%)	1 (<1%)	2 (1.0%)
Swelling face	0	1 (<1%)	1 (<1%)
Vomiting	2 (1.1%)	0	2 (1.0%)

Source: Study PKD_12_170, Table 16.2.7-1 and Study PKD_12_171, Table 16.2.7-1; Study PKD_11_033, Study PKD_11_034, Study PKD_11_271, Study PKD_11_272, Study PKD_11_348, and Study PKD_11_382, Appendix 11.2

¹ Considered to be a coding error; the correct preferred term is “muscular pain”.

Source: Clinical Summary, p.14

Please see Section 7.3.4 for further discussion of the adverse events seen in Sun’s pooled and pivotal bioequivalence studies.

7.4.2 Laboratory Findings

Across the eight pooled bioequivalence studies, 11 of 193 subjects (5.7%) who had post-study laboratory measurements completed, had one or more laboratory test parameters reported as an adverse event. Of these, 6 subjects had blood triglycerides increased, 3 subjects had blood sodium increased, and 3 subjects had aspartate aminotransferase increased and/or alanine aminotransferase increased. All were mild or moderate in intensity. Except for the elevation of blood sodium, these laboratory abnormalities can be seen with Pristiq. Repeat testing was done in all 11 subjects and all values returned to within normal range or to a value that was considered clinically insignificant.

These adverse events of abnormal post-study laboratory measurements are detailed in the Applicant's table below:

Table 25: ISS Laboratory Abnormalities Reported as Adverse Events
Listing of Subjects with Laboratory Abnormalities Reported as Adverse Events

Study No.	Subject No.	Parameter (unit)	Values		Intensity	Relationship
			Baseline (Screening /Check-In) ²	End of Study		
PKD_12_170	13 ¹	Sodium (mM)	134.04	156.19	Mild	Unlikely
	15 ¹	Sodium (mM)	142.38	157.22	Mild	Unlikely
	16	Triglycerides (mg/dL)	89.20	220.60	Mild	Possible
PKD_11_271	15	AST (U/L)	40.84	70.32 ³	Mild	Possible
		ALT (U/L)	49.61	101.46	Mild	Possible
		Triglycerides (mg/dL)	153.00	229.96	Mild	Possible
PKD_11_272	04	Triglycerides (mg/dL)	140.96	246.69 ³	Mild	Possible
	09	ALT (U/L)	25.12	146.52	Moderate	Possible
		AST (U/L)	34.48	131.44 ³	Moderate	Possible
	15	Triglycerides (mg/dL)	159.79	295.24	Mild	Possible
PKD_11_348	01	Sodium (mM)	140.88	152.32	Mild	Unlikely
	05	Triglycerides (mg/dL)	76.02	217.77	Mild	Possible
	07	ALT (U/L)	23.29	115.20	Mild	Unlikely
	08	Triglycerides (mg/dL)	136.96	304.51	Mild	Possible

Source: Study PKD_12_170 and Study PKD_12_171, Table 16.2.7-1 and Appendix 16.2.8; Study PKD_11_033, Study PKD_11_034, Study PKD_11_271, Study PKD_11_272, Study PKD_11_348, and Study PKD_11_382, Appendix 11.2 and Appendix 11.18

Note: With the exception of Subjects 13 and 15 in Study PKD_12_170, all subjects listed in the table above received all planned doses of study drug.

¹ Subjects 13 and 15 discontinued from Study PKD_12_170 after period I diarrhea; both subjects received only a single dose of Sun's Desvenlafaxine ER Tablets, 100 mg

² Liver function tests were not performed at Check-in; therefore, Screening values are reported

³ Value remained above the normal range at last follow-up

Source: ISS, p.13

Reviewer's Comment:

For the pivotal studies, there were only three subjects with lab abnormalities. Both Subject 13 and Subject 15 in Study 170 had elevated sodium. Both these subjects also discontinued due to the adverse event of diarrhea. It is possible that the elevated sodium is secondary to dehydration from the diarrhea.

7.4.3 Vital Signs

Vital signs (blood pressure, heart rate) were monitored during the course of the bioequivalence studies. On the day of dosing, testing was performed with subjects in a seated position pre-dose and 1, 2, 4, 8 (all except Study 170), 12, and 24 hours post-dose. Subjects were also evaluated for orthostatic changes by having them stand 7 to 8 hours post-dose. Results were within a clinically acceptable range as judged by the investigator. Clinically significant orthostatic hypotension (defined as a ≥ 20 mmHg decrease in systolic blood pressure and ≥ 10 mmHg decrease in diastolic blood

pressure) was not reported in any study. There was no effect on body temperature, measured on the day of dosing pre-dose and 4 and 12 hours post-dose.

Reviewer's Comment:

It should be noted that older subjects and subjects with hyper- or hypotension were excluded from Sun's pivotal bioequivalence studies.

7.4.4 Electrocardiograms (ECGs)

Desvenlafaxine has not been reported to be associated with ECG abnormalities. In a thorough QTc study, Pristiq did not cause QT prolongation.

Twelve-lead ECGs were obtained 6 to 8 hours post-dose in the Sun-sponsored bioequivalence studies. The ECGs were reviewed by the investigator. No clinically significant abnormalities were reported.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The Applicant notes that most of the adverse events from the pooled bioequivalence studies occurred following a 100 mg dose of desvenlafaxine in the fasted state. This is consistent with the Pristiq USPI that states that doses higher than 50 mg in the clinical trials were associated with a greater incidence of adverse reactions and discontinuations.

The Applicant's table below compares the adverse events by dose (fasted state):

Table 26: ISS TEAEs by Dose (Fasted State Only)
Non-Laboratory Treatment-Emergent Adverse Events by Dose (Fasted State Only)

Preferred term	N (%)	
	50 mg (N=61 ¹)	100 mg (N=89 ¹)
Abdominal pain	0	1 (1.1%)
Chills	0	1 (1.1%)
Convulsion	0	1 (1.1%)
Diarrhea	1 (1.6%)	16 (18.0%)
Diarrhea haemorrhagic	0	1 (1.1%)
Dizziness	0	2 (2.2%)
Dyspepsia	0	1 (1.1%)
Foaming at mouth	0	1 (1.1%)
Headache	0	2 (2.2%)
Hyperhidrosis	0	1 (1.1%)
Injection site pain ²	1 (1.6%)	0
Nausea	0	2 (2.2%)
Somnolence	0	2 (2.2%)
Vomiting	1 (1.6%)	1 (1.1%)

Source: ISS, p.10

7.5.2 Food Effect on Adverse Events

Despite an increase in C_{max} and AUC in the fed state for Desvenlafaxine ER 100 mg Tablets, all the adverse event reports of diarrhea occurred following a single dose in the fasted state for both the test and RLD product. In addition, most adverse events occurred when desvenlafaxine was dosed in the fasting state, as illustrated by the Applicant's table below:

Table 27: ISS TEAEs by Dosing Condition (Sun's Desvenlafaxine ER Tablets Only)
Non-Laboratory Treatment-Emergent Adverse Events by Dosing Condition (Sun's Desvenlafaxine ER Tablets Only)

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: ISS, p.9

7.5.3 Drug-Demographic Interactions

The Sun-sponsored studies were performed in healthy adult volunteers ranging in age from 19 to 49 years. All were Indian males. Therefore, no analyses of the effects of sex, races, or age are possible.

7.7 Additional Submissions/Safety Issues

120-Day Safety Report

On 24 July 2013, the Applicant submitted the 120-Day Safety Update which included updates to the Nonclinical Overview (Module 2.4), the Integrated Summary of Safety (Module 5.3.5.3), and the literature-references (Module 5.4).

Sun conducted a literature search on 28 May 2013 to support the 120-day Safety Update submission. The safety update search restricted results to publications available after 1 February 2013. The following databases were searched: Biosis Previews[®], EMBASE[®], MEDLINE[®], and ToxFile.

The search of the nonclinical literature identified 6 unique citations. All titles and abstracts were reviewed for information that could contribute significant nonclinical safety data. The search identified articles pertaining to the development of new bioanalytical methods and general review articles. According to the Applicant, no new nonclinical safety-related information was identified. Therefore, the Applicant proposes no changes to the nonclinical sections of the labeling other than replacing Pristiq[®] with Desvenlafaxine Fumarate Extended Release Tablets where applicable.

The search of the clinical literature identified a total of 35 citations. The majority of articles pertained to efficacy primarily in major depression but also for menopausal vasomotor symptoms. According to the Applicant, none described new safety information. Several publications described Pfizer-sponsored research conducted in support of the current approved labeling. One article of interest was identified for full review: a case report of myositis (unlabeled adverse event) temporally associated with desvenlafaxine therapy with positive dechallenge and rechallenge. The Applicant summarized the case as follows:

Stephens et al. (2012; Australia) report, in letter format only, myositis temporally associated with desvenlafaxine therapy with positive dechallenge and rechallenge.⁴ A 23-year old female was hospitalized for evaluation of bilateral pain, swelling, and loss of power in her upper arms, which had started the same day. Medical history was not contributory. The only medication listed was desvenlafaxine for mild depression

⁴ Stephens M, Rowland JTJ, Irani, AZ. Desvenlafaxine-induced myositis with positive medication rechallenge. Med J Aust 2012; 197(2): 91-92.

diagnosed 8 months earlier (50 mg/day for the first 4 months, and then 100 mg daily until presentation). On admission, her creatine kinase (CK) was 6970 IU/L (upper limit of the reference range, 145 IU/L). Venous thrombosis was ruled out; however, bilateral muscle edema was noted. Desvenlafaxine was stopped. Further investigations for the cause were normal. On Day 3 of admission, she developed prominent physical withdrawal symptoms and desvenlafaxine was resumed at 100 mg/day. Swelling of her forearms and upper arms and loss of muscle power were exacerbated, with increased pain and a rise in CK level. An adverse drug reaction was suspected and desvenlafaxine was tapered off and escitalopram started. Outpatient electromyography on Day 9 was consistent with upper limb myositis. She experienced no further adverse drug reaction on escitalopram.

The Applicant states that this new information does not alter the conclusions reached in the original ISS and that no new significant risks have been identified that warrant changes to the approved drug labeling.

Reviewer Comment:

Desvenlafaxine is the major active metabolite of the antidepressant venlafaxine (Effexor and Effexor XR). The current Effexor XR label describes the following rare musculoskeletal system adverse events observed during the premarketing evaluation of Effexor and Effexor XR: muscle cramp, muscle spasms, musculoskeletal stiffness, and myopathy. The Postmarketing Reports section of the Effexor and Effexor XR labels also list CPK increased and rhabdomyolysis as adverse events.

8 Postmarket Experience

There is no postmarketing experience with this product.

9 Appendices

9.1 Literature Review/References

Sun had proposed to include updates of the published literature, spontaneous postmarketing reports, and any other available pertinent safety information relative to the labeling of the approved reference product with the NDA submission. Given that safety and efficacy data changes to the label for the reference product were recently approved (14 February 2013), the Applicant stated that an update at the time of NDA submission was not necessary, but would be provided with the 120-Day Safety Update (see Section 7.7).

9.2 Labeling Recommendations

The proposed labeling for Desvenlafaxine Extended Release Tablets is based on the current Pristiq® label.

Table 28: Applicant's Proposed Changes to Approved Labeling
Proposed Changes to Clinical Pharmacology Section of the Approved Labeling for Desvenlafaxine (Dosing with Meals)

Section	Pristiq®	Desvenlafaxine Extended Release Tablets
12.3	<p>Absorption and Distribution A food-effect study involving administration of PRISTIQ to healthy subjects under fasting and fed conditions (high-fat meal, 800 to 1000 calories) indicated that desvenlafaxine C_{max} was increased about 16% in the fed state, while the AUCs were similar. This difference is not expected to be clinically significant; therefore, PRISTIQ can be taken without regard to meals [see Dosage and Administration (2.1)].</p>	<p>Absorption and Distribution A food-effect study involving administration of <i>Desvenlafaxine Extended Release Tablets</i> to healthy subjects under fasting and fed conditions (high-fat meal, 800 to 1000 calories) indicated that desvenlafaxine C_{max} was increased about (b) (4)% in the fed state, while the (b) (4) AUC was increased about 29%. (b) (4) These differences are (b) (4) not expected to be clinically significant; (b) (4) <i>Desvenlafaxine Extended Release Tablets</i> can be taken without regard to meals [see Dosage and Administration (2.1)].</p>

Reviewer comment: OCP has changed the (b) (4) % to 37%.

Sun also proposes to add product-specific pharmacokinetic information for the 50-mg tablet of Desvenlafaxine ER Tablets; this information is missing from the label of Pristiq®.

Proposed Changes to Clinical Pharmacology Section of the Approved Labeling for Desvenlafaxine (Pharmacokinetic Profile)

Section	Pristiq®	Desvenlafaxine Extended Release Tablets
12.3	<p>Pharmacokinetics</p> <p>The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of 100 to 600 mg/day. With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4-5 days. At steady-state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.</p>	<p>Pharmacokinetics</p> <p>The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of (b) (4) to 600 mg/day. (b) (4)</p> <p>(b) (4)</p> <p>(b) (4) With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4-5 days. At steady-state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.</p>

Reviewer comment: OCP has recommended the following alternative labeling for this section:

<p>12.3 Pharmacokinetics</p> <p>The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of 100 to 600 mg/day. With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4 to 5 days. At steady-state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.</p> <p>The mean terminal half-life, $t_{1/2}$, of desvenlafaxine after administration of this desvenlafaxine extended-release-tablets is about 9.8 hours. The median (range) time to peak concentration (T_{max}) is 7.5 (4.5 – 14.0) hours after administration of 50 mg desvenlafaxine extended-release tablets.</p> <p><u>Absorption and Distribution</u></p> <p>This desvenlafaxine extended-release 50 mg and 100 mg demonstrated similar exposures (C_{max}, AUC) to a 50 mg and 100 mg extended-release desvenlafaxine succinate product, respectively.</p>

The current labeling for Pristiq® indicates that *in vitro*, desvenlafaxine is not an inhibitor of the P-gp transporter. Newly identified published information indicates that *in vitro*, desvenlafaxine induces expression of the P-gp transporter and BCRP at clinically relevant concentrations, however, based on an *in vivo* drug-drug interaction study, there was no effect on a P-gp substrate, indinavir.

**Proposed Changes to Clinical Pharmacology Section of the Approved Labeling for
 Desvenlafaxine: Clinical Pharmacology (Interactions with P-gp)**

Section	Pristiq [®]	Desvenlafaxine Extended Release Tablets
12.3	Drug interaction Studies (para 6) <i>In vitro</i> , desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of desvenlafaxine are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter.	Drug interaction Studies (para 6) <i>In vitro</i> , desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of desvenlafaxine are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter. Desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. (b) (4) (b) (4)

Reviewer comment: Because this clinical study used Pristiq, this information cannot be included in this label. In addition, no significant information is added by this statement.

DMEPA Recommendations

Loretta Holmes from the Division of Medication Error Prevention and Analysis (DMEPA) in her 16 September 2013 review had the following recommendations for the Division for labeling:

In the Highlights of Prescribing Information, *Dosage Forms and Strengths* and Full Prescribing Information, *2.3 Discontinuing Desvenlafaxine Extended-Release Tablets* sections of the insert labeling, there are instances where the numerical strength is not followed by its unit of measure (i.e., "...50 and 100 mg tablets" and "50 to 400 mg", respectively). We recommend revising such that the numerical strength is followed by its unit of measure (e.g., 50 mg and 100 mg tablets and 50 mg to 400 mg). DMEPA also had the following recommendations for the Applicant for the container labels (50 mg, 100 mg) to be implemented prior to the approval of the NDA:

The Medication Guide (MG) statement reads: (b) (4). We recommend replacing the proposed statement with the following language "Dispense the accompanying Medication Guide to each patient" [see 21 CFR 208.24(d)]. Additionally, provide the Medication Guides in sufficient numbers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the product [21 CFR 208.24(b)(1)(2)].

9.3 Advisory Committee Meeting

No advisory committee meeting is planned because there are no controversial issues in this application. The application is based on bioequivalence studies. Desvenlafaxine is not a new molecular entity; there is considerable premarket and postmarketing experience with desvenlafaxine.

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

/s/

CHRISTINA P BURKHART
12/18/2013

ROBERT L LEVIN
12/18/2013
Please see cross-discipline review memo to follow.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			2 pivotal bioequivalence studies (Studies 170 and 171)
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	All subjects in the pivotal studies were Asian (Indian) males. 505(b)(2):Applicant relying on efficacy data from RLD.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			x	505(b)(2): TQT Study negative for RLD
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	RLD label was recently updated. Applicant plans further update with 120-Day Safety Update.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Applicant requesting waiver.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	All subjects in the pivotal studies were Asian (Indian) males. 505(b)(2):Applicant relying on data from RLD.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical 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.

There are no potential review issues at this time.

Christina P. Burkhart, M.D.

5/9/2013

Reviewing Medical Officer

Date

Robert L. Levin, M.D.

Clinical Team Leader

Date

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

/s/

CHRISTINA P BURKHART
05/09/2013

ROBERT L LEVIN
05/20/2013