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APPLICATION NUMBER:

205583Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review Memo

Date	January 22, 2014
From	Robert L. Levin, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	205583
Therapeutic Class	Antidepressant; Serotonin-Norepinephrine Reuptake Inhibitor
Sponsor	Sun Pharma Global FZE, United Arab Emirates
Submission Date	March 28, 2013
Related IND	113361
Established name / Tradename	Desvenlafaxine Fumarate Extended Release Tablets; Tradename: Desvenlafaxine Extended Release Tablets
Dosage forms / strength	Oral Extended Release Tablets; 50 mg and 100 mg
Proposed Indication	Major Depressive Disorder
Recommendation:	Approval

1. Introduction to the Review

On March 28, 2013, Sun Pharmaceutical submitted NDA 205583 for Desvenlafaxine Fumarate Extended-Release Tablets for the treatment of major depressive disorder (MDD). This is a 505(b)(2) application relying on efficacy and safety data from the innovator product, desvenlafaxine succinate extended-release tablets (Pristiq, NDA 21992), which was approved in February 2008 for the treatment of MDD. Desvenlafaxine is the major active metabolite of venlafaxine, and it is a serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant. The proposed product is a new fumarate salt of desvenlafaxine; it is an extended-release product. The primary data from the application derive from two pivotal bioequivalence studies comparing the pharmacokinetic profiles of the proposed product and the reference listed drug, desvenlafaxine succinate (Pristiq). In addition, the sponsor has submitted chemistry, manufacturing, and controls (CMC), biopharmaceutics, and microbiology data to support the application. The sponsor did not conduct efficacy and safety studies with the product. There are no nonclinical data in the application. Reviewers from all disciplines have concluded that the data support approval of the application, and there are no unresolved issues. I agree with the conclusions and recommendations of all reviewers, and I recommend approval of the application.

2. Background/Regulatory History/Foreign Regulatory Actions

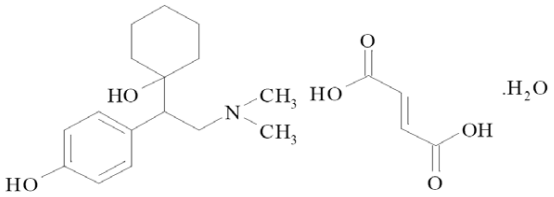
The sponsor requested a pre-IND meeting (under IND 113361) in September 2011 to discuss the development plans for the product, and they provided a detailed meeting package. The Division provided preliminary comments on the sponsor‘s plan for the submission of an NDA. The sponsor cancelled the meeting, because the Division provided adequate comments. We reached agreement on the design of the bioavailability and bioequivalence studies which would support the application.

3. ONDQA - Chemistry Manufacture and Controls (CMC)

Shastri Bhamidipati, Ph.D. from the Office of New Drug Quality Assessment (ONDQA) performed the CMC review. Dr. Bhamidipati reviewed the detailed data from the formulation, pharmaceutical, and manufacturing process development studies. He reviewed data on the following: manufacture processes, control of excipients, control of drug product, control of drug product, reference standards and materials, container closure system, stability, facilities and equipment, and establishment evaluation report. He also reviewed labeling and provided labeling recommendations. Dr. Bhamidipati concluded that the CMC data on the drug substance and drug product are adequate and support approval of the application. He concluded that there are no unresolved CMC issues. Dr. Bhamidipati does not recommend any postmarketing commitments. I agree with Dr. Bhamidipati's conclusions and recommendations.

Drug Substance Description and Data

The chemical name of the drug substance is: (±) 4-[2-dimethylamino-1-(1-hydroxycyclohexyl)-ethyl]-phenol fumarate Monohydrate. The molecular formula is: $C_{16}H_{25}NO_2$. $C_4H_4O_4$. H_2O. The molecular weight is 397.45. The structure is presented below:



Desvenlafaxine fumarate monohydrate is a white, off-white powder with one chiral center and is synthesized as a (b) (4). The solubility of desvenlafaxine base is pH-dependent with maximum solubility of 31 mg/mL in 0.1N Hydrochloric acid. The sponsor referred to Type II DMF #26615 for all chemistry, manufacturing and controls information of Desvenlafaxine fumarate monohydrate through a letter of authorization from the DMF holder, Sun Pharmaceuticals. The DMF has been reviewed and deemed adequate to support this NDA. Desvenlafaxine fumarate monohydrate is (b) (4) and characterized by (b) (4). The drug substance has been analyzed at the drug product manufacturing site for identification, assay, related impurities, bulk and tapped densities, and particle size ascertaining its suitability for use. The stability of the drug substance was stated to have been adequately established by the DMF holder with a retest date of (b) (4) months from the time of manufacturing.

Drug Product Description and Data

Desvenlafaxine fumarate extended-release tablets are light pink (50 mg strength) or brick red(100 mg strength) , circular, biconvex, beveled edge film-coated tablets, imprinted with '747' (50 mg strength) and '804'(100 mg strength) in black ink on one side and plain on the other side. Each tablet contains 72.035 mg or 144.07 mg of desvenlafaxine fumarate equivalent to 50 mg or 100 mg of desvenlafaxine. The tablets are supplied in

HDPE bottles of 30 and 90 counts with Child Resistant Cap and bottles of 100c count with Non Child Resistant Cap. The drug product is stored at 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F) [USP Controlled Room Temperature]. The recommended dose is 50 mg once daily taken orally with or without food. The tablets should be taken intact without splitting, crushing, chewing or dissolving.

Therefore, ONDQA recommends a shelf-life of 12 months for expiration dating of the drug product, based on the 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.

The commercial drug product will be manufactured by Sun Pharmaceuticals, Halol, India and distributed by Caraco Pharmaceutical Laboratories, Detroit, MI.

Compliance Inspection

The Office of Compliance has provided an overall acceptance recommendation for of all the manufacturing sites for this NDA. OC filed an Establishment Evaluation System (EES) review.

4. Nonclinical Pharmacology/Toxicology

Shiny V. Mathew, Ph.D. performed the nonclinical pharmacology/toxicology review. No new nonclinical pharmacology or toxicology data were submitted in this application. However, the sponsor's nonclinical summary indicates that a literature search was conducted on four databases (Biosis Previews®, EMBASE®, MEDLINE® and Toxfile) on May 28, 2013, which yielded six unique citations. The sponsor reviewed these citations and found that there were no new data that could contribute significantly to nonclinical safety related information. The literature citations were not provided within the submission. The sponsor does not propose any changes to nonclinical sections of the label, other than replacing PRISTIQ® with Desvenlafaxine Fumarate Extended-Release Tablets, where applicable.

No impurities, degradants, or novel excipients in Desvenlafaxine Fumarate Extended Release tablets have been identified at this time that would require additional toxicological characterization. Dr. Mathew concluded that there are no Pharmacology/Toxicology issues that would prevent the approval of this NDA. There are no unresolved nonclinical issues. I agree with Dr. Mathews' conclusions and recommendations.

5. ONDQA Biopharmaceutics

Elsbeth Chikhale, Ph.D. performed the biopharmaceutics review. Dr. 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: %
• 8 hours: %
• 16 hours: NLT (b) (4)%

Dr. Chikhale recommends a postmarketing commitment regarding the development of an optimal discriminating dissolution method. She provided the following language regarding the PMC to communicate to the sponsor:

- *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 there was no dose dumping as demonstrated in the *in vitro* alcohol dose dumping study. She also concluded that the data support the sponsor's claim that the product is an extended-release product (for the 50 mg and 100 mg tablets).

Dr. Chikhale concluded that there are no unresolved premarketing issues, and she supports approval of the NDA. As noted, she recommends the postmarketing commitment specified above. I agree with Dr. Chikhale's conclusions and recommendations.

6. Office of Clinical Pharmacology

Kofi Kumi, Ph.D. performed the clinical pharmacology review (filed on December 22, 2013). Dr. Kumi concluded that desvenlafaxine fumarate extended-release tablets are bioequivalent to the reference listed drug, desvenlafaxine succinate extended-release tablets (Pristiq®) for the 50 mg and 100 mg strengths, under fasting conditions. He also concluded that desvenlafaxine fumarate extended-release tablets can be administered

with or without food. In addition, he concluded that the product exhibits extended-release characteristics similar to Pristiq, as supported by the *in vivo* pharmacokinetic profile. Dr. Kumi concluded that the data are adequate, and he recommends approval of the NDA. There are no unresolved clinical pharmacology issues. Dr. Kumi provided numerous recommendations for labeling, which the Division and the sponsor have accepted. The OCP reviewers do not recommend any postmarketing commitments. I agree with Dr. Kumi's conclusions and recommendations.

Description of the Clinical Bioavailability and Bioequivalence Studies

The sponsor conducted a total of eight bioavailability or bioequivalence studies in a total of 194 healthy male subjects. Of these, five were pilot studies to develop various formulations, and one was a pilot study of the final formulation. There were two pivotal bioequivalence studies. The sponsor also conducted multimedia *in vitro* dissolution testing and *in vitro* dissolution in alcoholic media, consistent with the Agency's recommendations and requirements. The table below summarizes the designs of the three studies conducted with the final formulation, including the 2 pivotal bioequivalence studies.

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

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 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. 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.

Bioequivalence Study Results

Desvenlafaxine fumarate Extended Release (ER) tablet was demonstrated to be bioequivalent to Pristiq® (Desvenlafaxine succinate) ER Tablet under fasting conditions for the 50 mg and 100 mg strengths, respectively. Tables 1 through 4 summarize the statistical results for the comparison of desvenlafaxine fumarate ER (T) to Pristiq (R) 50 mg and 100 mg ER tablets under fasting and fed conditions. The 90% confidence intervals calculated from the Ln-transformed data on the least square means ratios (test/reference) for AUC0-t, AUC0-inf and Cmax values were within the limits of 80.00% to 125.00%.

However, Dr. Kumi notes that the 90% CI did not include 100 and was on the lower end of the confidence interval. The exposure to desvenlafaxine after administration of the Desvenlafaxine ER 50 mg tablet was approximately 10% lower than that observed after administration of Pristiq ER 50 mg tablet. The median Tmax was about one hour longer after administration of Desvenlafaxine fumarate ER 50 mg than the Tmax observed after administration of Pristiq ER 50 mg. These differences are not expected to be clinically relevant. There was no significant difference in half-lives between the test and reference products.

Table 1: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Treatments A or B to Healthy Subjects under Fasting Conditions (N=33)

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

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

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

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

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

Table 3: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters after a Single Oral Dose of Treatments A or B to Healthy Subjects under Fasting Conditions (N=33)

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

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

Table 4: Summary of statistical Desvenlafaxine after administration Desvenlafaxine fumarate ER (SUN) with food and Pristiq ER 100 mg without food

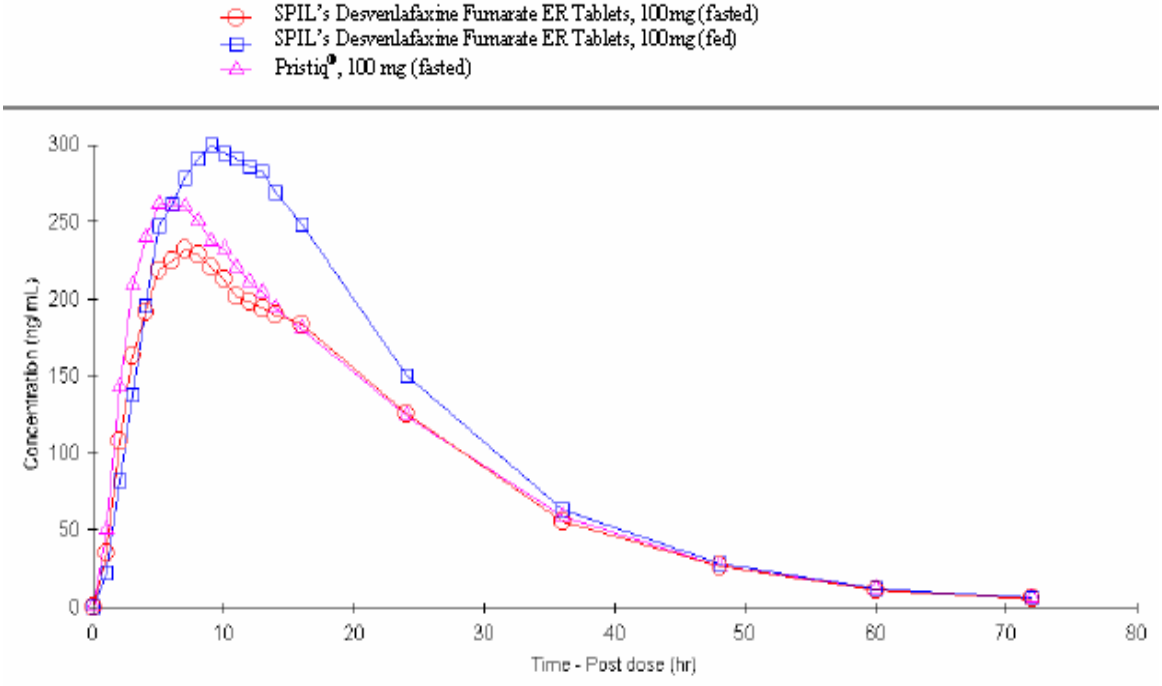
Parameter	Geometric Mean		Ratio of Mean (%)	90% Confidence Interval
	Treatment B (n=33)	Treatment C (n=33)	B/C	
Cmax (ng/mL)	332.63	271.70	122.43	115.03 – 130.29
AUCt (ng*hr/mL)	6963.70	5961.82	116.80	107.75 – 126.62
AUC∞ (ng*hr/mL)	7047.88	6045.28	116.58	107.51 – 126.43
Tmax [hr][*]	9.5 (4.0 – 16.0)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

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

Food Effect Studies

Figure 1 illustrates the plasma concentration-time profile after administering desvenlafaxine fumarate 100 mg under fed and fasting conditions. The figure also includes data after the administration of Pristiq under fasting conditions. When desvenlafaxine fumarate 100 mg was administered under fed conditions, the Cmax increased by 37%, and the AUC increased by 29% (compared to administration under fasting conditions. In separate studies with Pristiq, there was also a food effect, although to a lesser extent; under fed conditions, the Cmax increased by 16%; but there was no significant increase in AUC. The OCP team has concluded that the food effect with desvenlafaxine fumarate is not clinically significant, and the differences in food effects between the two products are not clinically significant.

Figure 1: Mean plasma desvenlafaxine concentration time profile after administration of 100 mg Desvenlafaxine fumarate ER and Pristiq ER



Alcohol Dose Dumping

There was no dose dumping with alcohol, based on results of an *in vitro* study.

Clinical and Bioanalytical Site Inspections

The Office of Scientific Investigations (OSI) audited the bioequivalence studies and inspected the study sites. The OSI inspector reported to the Division that there were no issues that would prevent a recommendation of approval of the NDA. The reviewer has filed his review.

7. Clinical Review

Christina Burkhart, M.D. performed the clinical review. She reviewed data from 8 pharmacokinetic bioavailability studies, including the two pivotal bioequivalence studies (Studies 170 and 171). Dr. Burkhart concluded that the sponsor conducted adequate safety assessments and submitted adequate safety data. She also concluded that there were no new, unexpected, or significant safety findings with the desvenlafaxine fumarate formulation, compared to the know safety profile of Pristiq (desvenlafaxine succinate ER) or other desvenlafaxine drug products. Dr. Burkhart concluded that there are no unresolved clinical or other issues, and she recommends approval of the application. I agree with Dr. Burkhart's conclusions and recommendations.

A total of 194 healthy adult Asian male subjects 19 t 49 years of age were exposed to at least one dose of either the sponsor's desvenlafaxine fumarate formulations or the reference listed product, desvenlafaxine succinate extended-release tablets (Pristiq). Of these, 106 subjects were treated with Sun's proposed final formulation. Dr. Burkhart concluded that the various formulations were sufficiently similar to allow pooling of the safety data.

Overall, few adverse events were reported. There were no deaths in the studies. One subject had a serious adverse event (acute gastroenteritis, diarrhea, epigastric pain, dehydration, and fever) 3 days after treatment with a single dose of desvenlafaxine fumarate. It is possible that the event was related to treatment. Another subject had an SAE (convulsion) following a single dose of Pristiq 100 mg. 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; diarrhea was 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%). There was no imbalance in adverse events between study drug treatments.

There were no significant vital sign, ECG, or clinical laboratory findings.

Dr. Burkhart reviewed the 120-day safety update, which included updates to the Nonclinical Overview, the Integrated Summary of Safety, and a review of the literature regarding desvenlafaxine. There were no significant safety findings.

Dr. Burkhart agrees with the other reviewers. Contributed labeling recommendations, and agrees with reviewers in all other disciplines.

8. Microbiology Review

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.

9. DMEPA Review

Loretta Holmes, BSN, Pharm.D. performed the review for the Division of Medication Error Prevention and Analysis. DMEPA reviewed the sponsor's proposed labels and also compared them with the currently approved labels of the innovator product (Pristiq), in

order to assess whether were any areas of vulnerability that could lead to medication errors. DMEPA also searched the FDA Adverse Event Reporting System (FAERS) database for Pristiq medication errors that could potentially inform the NDA review. The FAERS search did not identify any new signals. The DMEPA review team provided a number of revisions in product labeling to improve the clarity of labeling and to promote the safe use of the product and mitigate any confusion that can lead to medication errors. The Division has accepted all of Dr. Holmes' recommendations.

10. OPDP Review

Nazia Fatima, Pharm.D, MBA, Regulatory Review Officer from the Office of Prescription Drug Promotion (OPDP) performed the review. OPDP reviewed the draft product labeling (PI), carton/container labelling and medication guide (MG) for desvenlafaxine fumarate extended-release tablets. OPDP has no comments regarding product labeling, the medication guide, or the carton/container labeling submitted by the sponsor on March 28, 2013.

11. Patient Labeling Team Review

Sharon W. Williams, MSN, BSN, RN reviewed the sponsor's proposed label and medication guide. She conducted a collaborative review with Dr. Fatima from OPDP. Dr. Williams has recommended several minor revisions to the medication guide. The Division has accepted these revisions.

12. Labeling Review

All review disciplines reviewed the label and provided recommendations on revisions. The label for this product was based on the currently approved label for Pristiq. We revised numerous sections of the sponsor's proposed label. On January 17, 2014 we reached agreement with the sponsor on labeling.

13. Pediatric Use/PREA Waivers/Deferrals

The application triggers PREA because the product is a new dosage form. The sponsor requested a (b) (4) of the requirement to conduct pediatric studies with Desvenlafaxine Extended Release Tablets under the Pediatric Research Equity Act (PREA; Section 505A of the Federal Food, Drug, and Cosmetic Act) in children and adolescents (0 to 17 years of age). (b) (4)

The Division presented the sponsor's request and rationale to the PeRC on December 4, 2013. The Division recommended granting a partial waiver for studying children 0 to 6 years of age with MDD, because studies are impossible or highly impractical. The diagnosis of MDD is difficult to establish before age 7, and the prevalence of MDD is quite low in this age group. In addition, antidepressant medication treatment is not the

recommended first-line treatment for this sub-population. We recommended granting a deferral for pediatric studies in MDD in children 7 to 17 years of age, because the product is ready for approval in adults. The PeRC agreed with the recommendations. The Agency will grant the partial waiver and deferral.

14. Conclusions and Recommendations

I recommend approval of the NDA.

Postmarketing Commitment:

The Agency will require the sponsor to obtain additional biopharmaceutics data. Dr. Chikhale has provided the following language to communicate to the sponsor:

- *You must 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, you 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, you must 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.*

Required PREA Study:

The sponsor must conduct a pediatric study under PREA. This must be an adequate and well controlled, randomized, double-blind, placebo-controlled study to formally assess the efficacy and safety of desvenlafaxine fumarate extended-release tablets in the treatment of pediatric patients aged 7 to 17 years with a diagnosis of major depressive disorder.

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/s/

ROBERT L LEVIN
01/22/2014