CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205208Orig1s000

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA 205208 (10)

Sponsor:	Teva Pharmaceuticals USA
Drug(s):	Desvenlafaxine fumarate Extended-Release Tablets 50 mg and 100 mg base
Indication:	Major Depressive Disorder (Adults)
Material Submitted:	Pediatric Plan
Correspondence Date:	September 10, 2013
Date Received:	September 10, 2013

I. Background of Pediatric Plan:

As noted in Medical Officer's Primary Review, dated September 05, 2013, sponsor had previously requested a Full-Waiver for studies in all pediatric ages. The Division had informed them that we would grant a Partial Waiver only for children age 0-6 years of age with MDD and a Deferral for MDD studies in children (7-11 years old) and adolescents (12-17 years old) as long as we receive a proposal for such studies. At the time of that review, no proposal had been received by DPP.

By way of the present submission, the sponsor has submitted requests for a waiver for pediatric studies for children less than 7 years and for deferral for children (ages 7 - 11 years) and adolescents (ages 12 – 17 years). The basis provided for the requested waiver in children less than 7 years is the impracticality of such studies because of the low prevalence and inability to reliably diagnose MDD in such age groups. The basis provided for the requested deferral in children 7-17 years is that: "The drug or biological product is ready for approval for use in adults before pediatric studies are complete (section 505B (a)(3)(A)(i)(I) of the Act)." A description of the planned pediatric studies is included which is summarized below. They have suggested the following deferral dates: Protocol Submission Date: June 30, 2018; Study Completion Date: December 31, 2024; and Study Report Submission: June 25, 2025.

Proposed Pediatric Study: An 8 week, randomized, double-blind, placebo-controlled, fluoxetine-referenced, parallel-group study in children ages 7-11 years and adolescents 12-17 years with MDD (CDRS-R score >40) with a dose of 50 mg/day of desvenlafaxine fumarate extended-release tablets. Proposed primary efficacy endpoint would be the change from baseline to Week 8 in the Child Depression Rating Scale – Revised (CDRS-R): Total Score.

II. Conclusions and Recommendations

1. Sponsor's request for a pediatric waiver for studying MDD in children less than 7 years of age should be accepted.

2. Sponsor's proposal for a pediatric study should be modified. There needs to be two pediatric studies (e.g. single studies in 7-11 and 12-17 years old).

3. Acceptability of the specific deferral dates will be determined by PERC.

Glenn B. Mannheim, MD
Medical Officer
September 11, 2013

CC:
NDA 205208 (09, 010)
G Mannheim
K Ansah
J Zhang
M Mathis

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

/s/

GLENN B MANNHEIM
09/11/2013

JING ZHANG
09/12/2013

CLINICAL REVIEW

Application Type	NDA, 505(b) (2)
Application Number(s)	N 205208
Priority or Standard	Standard
Submit Date(s)	December 13, 2012
Received Date(s)	December 13, 2012
Filing Meeting	January 31, 2013
PDUFA Goal Date	October 13, 2013
Division / Office	OND I/DPP
Reviewer Name(s)	Glenn Mannheim, M.D.
Review Completion Date	September 05, 2013
Established Name	Desvenlafaxine
(Proposed) Trade Name	Desvenlafaxine (b) (4) Extended-Release Tablets 50 mg and 100 mg base
Therapeutic Class	Antidepressant: selective serotonin and norepinephrine reuptake inhibitor (SNRI)
Applicant	Teva Pharmaceuticals USA
Formulation(s)	Extended-Release Tablets
Dosing Regimen	50 mg and 100 mg
Indication(s)	Major Depressive Disorder
Intended Population(s)	Major Depressive Disorder (Adults)

Clinical Review
Glenn Mannheim, M.D.
NDA 205208, 505(b) (2)
Desvenlafaxine fumarate Extended-Release Tablets 50 mg and 100 mg

I. Background:

Pristiq (NDA 21-992), a desvenlafaxine succinate salt, is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), which was approved on February 29, 2008 for the treatment of major depressive disorder (MDD) at a recommended single daily dose of 50 mg. Under IND 113,629, Teva Pharmaceuticals USA had teleconferences with FDA on December 6, 2011 and October 16, 2012 to discuss a proposed 505(b) (2) application for Desvenlafaxine (Base) Extended-Release (ER)Tablets 50 mg and 100 mg using a different salt (desvenlafaxine fumarate) and using Pristiq as the reference listed drug. Three pharmacokinetic studies [fasting (Study 53711) and effect of food (Study 53811) on the 100 mg ER tablets; and fasting and effect of food (Study 2012-2883) on the 50 mg ER tablets] and reliance upon FDA's previous finding of safety (and efficacy) for Pristiq®, including the non-clinical data as described in Pristiq® labeling was determined to be adequate.

II. Materials Reviewed

Bioequivalence Studies 53811 (100 mg Fed Study) and 53711 (100 mg Fasting Study)
Bioavailability Study 2012-2883Proposed Labeling
Financial Disclosure Certification
Debarment Certification

No desvenlafaxine clinical literature or Case Report Forms were included in this submission.

III. Review of Clinical Safety Data

Study 53811: This was an open-label, single-center, randomized, single-dose, two-period, two-treatment, two-sequence crossover study to compare the bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets, 100 mg to Pristiq® Extended-Release Tablets, 100 mg under fed conditions in healthy adult human subjects.

This study was conducted to assess the bioequivalence of the test formulation of Desvenlafaxine Fumarate ER Tablets, 100 mg, to Pristiq® ER Tablets, 100 mg in 24 healthy, adult, human subjects under fed conditions. Additional objective of the study was to monitor the safety of the subjects.

Dose and Mode of Administration

After an overnight fast of at least 10 hours, all subjects consumed a high-fat breakfast, 30 minutes before receiving a single dose of study medication. Standard meals were then provided at approximately 4 and 10 hours after study drug administration and at appropriate times thereafter. There were two dosing periods with a minimum washout of 7 days between each dose administration. Subjects were randomized into one of two treatment sequences: AB or BA. Treatment A was Teva's, Desvenlafaxine Fumarate ER Tablets, equivalent to 100 mg desvenlafaxine, Test Formulation. Treatment B was Pristiq® ER Tablets, 100 mg.

Blood samples for desvenlafaxine were taken at the following times, per protocol: within 1 hour (2 pre-dose samples) of dosing, and at 1.5, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12, 14, 16, 24, 36, 48, and 60, hours after dosing.

Safety Data for Study 53811
This study enrolled 24 healthy, adult subjects (mean age of 37.7 years, 54 % females, 87 % white with average BMI of 25). No additional subjects were enrolled. Only 22 subjects completed the study. Subject numbers 5 and 13 were withdrawn by the investigator/sponsor for emesis. These subjects were not included in the pharmacokinetic analysis population.

No deaths or serious AEs were reported during the course of the study.

Twelve (12) subjects reported 33 adverse events of mild intensity. They consisted of headache (n = 7), nausea (n = 11), anxiety (n = 3), visual disturbance (n = 2) and emesis (n = 1), diarrhea (n = 1), dizziness (n = 1), stomach cramps (n = 1), bilateral jaw paresthesia (n = 1), diaphoresis (n = 1), trembling in legs (bilateral) (n = 1), weakness in legs (bilateral) (n = 1), blurred vision (n = 1) and swelling in right eye (n =1). The number of subjects with headache (A: 3, B: 4), nausea (A: 6, B: 5) and anxiety (A: 1, B1) were similar between those who received Desvenlafaxine Fumarate ER (Treatment A) compared to those receiving Pristiq (Treatment B).

Physical exams and ECGs were performed at screening. Sitting vital signs (blood pressure, pulse, and temperature) were assessed at screening, within 2 hours prior to each study drug administration, 2 hours after each study drug administration, and with End of Study/Early Termination Procedures. There were no clinically significant changes in any laboratory or vital sign parameters noted for any subject throughout this clinical trial.

Conclusion for Study 53811: In general desvenlafaxine fumarate ER tablet, 100 mg was well tolerated in this study. Adverse events of Desvenlafaxine Fumarate ER (Treatment A) were of a similar type and magnitude when compared to Pristiq (Treatment B).

Study 53711 : This was an open label, balanced, randomized, two-treatment, three-period, three-sequence, single oral dose, crossover study to evaluate bioequivalence of Desvenlafaxine (Base) Extended-Release Tablets 100 mg under fasting conditions and evaluation of food effect by relative bioavailability of Desvenlafaxine (Base) Extended-Release Tablets 100 mg under fasting and fed conditions in healthy adult human subjects.

Dose and Mode of Administration
After an overnight fast of at least 10 hours, all subjects received a single dose of study medication. Standard meals were then provided at approximately 4 and 10 hours after study drug administration. There was a minimum washout of 7 days between each dose administration. Subjects were randomized into one of two treatment sequences: AB or BA. Treatment A was Teva's, Desvenlafaxine Fumarate ER Tablets, equivalent to 100 mg desvenlafaxine, Test Formulation. Treatment B was Pristiq® ER Tablets, 100 mg.

Blood samples for desvenlafaxine were taken at the following times, per protocol: within 1 hour (2 pre-dose samples) of dosing, and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9,10, 11, 12, 14, 16, 24, 36, 48, and 60 hours after dosing.

Safety Data for Study 53711
There were no deaths or serious adverse events reported during the clinical trial period.

Thirty four (34) subjects were enrolled in the study, of whom 27 completed the study. Five (5) subjects [subject numbers: 6, 8, 27, 29 and 31] were withdrawn by the investigator/sponsor for emesis and two (2) subjects voluntarily discontinued from the study during Period I [subject numbers: 9 and 28]. Of the subjects withdrawn by the investigator/sponsor, subjects 8, 27 and 31 had emesis and nausea with Treatment A (Desvenlafaxine Fumarate ER) and subject 6 had headache, emesis and nausea with Treatment A and nausea with Treatment B (Pristiq). Of the two subjects (9 and 28) who voluntarily discontinued from the study, both had nausea with Treatment B.

Twenty-four (24) subjects reported 62 adverse events of mild to moderate intensity. They consisted of headache (n =11), nausea (n =21), emesis (n=8), diarrhea (n=4), dry mouth (n=2), restlessness (n=2), lightheaded (n=2), difficulty concentration (n=1), loss of appetite (n=1), somnolence (n=1), restless in legs (n=1), syncope (n=1), fever (n=1), stomach pain (n=1), shakiness (n=1), disorientation (n=1), anorexia (n=1), dizziness (n=1) and, soreness in left hand. There was a numerical excess of the following adverse events in subjects who received Desvenlafaxine Fumarate ER (Treatment A) compared to subjects receiving Pristiq (Treatment B): nausea (A: 12, B: 9), emesis (A: 6, B: 2), and dry mouth (A: 2, B: 0). There was a numerical excess of the following adverse events in subjects who received Pristiq (Treatment B) compared to Desvenlafaxine Fumarate ER (Treatment A): headache (B: 6, A: 4) and diarrhea (B: 3, A: 1). Otherwise, the overall adverse events were similar between the two groups.

Physical exams and ECGs were performed at screening. Sitting vital signs (blood pressure, pulse, and temperature) were assessed at screening, within 2 hours prior to each study drug administration, 2 hours after each study drug administration, and with End of Study/Early Termination Procedures. These measurements and physical assessments did not present any clinically significant findings. No subject experienced a clinically significant change in any of their laboratory values during the course of this study

Conclusion for Study 53711: There appears to be a slight numerical excess of nausea (A: 12, B: 9) and emesis (A: 6, B: 2) in subjects who received Desvenlafaxine Fumarate ER (Treatment A) compared to subjects who received Pristiq (Treatment B) when taken on an empty stomach. However, the numbers are too small to make any meaningful conclusions. In general desvenlafaxine fumarate ER tablet, 100 mg was well tolerated in this study.

Study 2012-2883:
This was an open-label, single-dose, randomized, three-period, six-sequence, three-treatment, crossover, comparative bioavailability study. The primary objective of this study was to evaluate the comparative bioavailability between Desvenlafaxine Fumarate (equivalent to 50 mg

desvenlafaxine) Extended Release Tablets (Teva Pharmaceuticals USA) and Pristiq® 50 mg Extended Release Tablets (Wyeth Pharmaceuticals Inc., USA) after a single-dose in healthy subjects under fasting conditions. The secondary objective of was to evaluate the effect of food on Desvenlafaxine Fumarate (equivalent to 50 mg desvenlafaxine) Extended Release Tablets from Teva Pharmaceuticals USA after a single-dose in healthy subjects under fasting and fed conditions.

Dose and Mode of Administration

Test Product (Treatment A and Treatment B): Desvenlafaxine Fumarate (equivalent to 50 mg desvenlafaxine) Extended Release Tablets (Teva Pharmaceuticals USA)

- Treatment A: [one tablet administered after an overnight fast of at least 10 hours]
- Treatment B: [one tablet administered 30 minutes after the start of a high fat, high calorie breakfast, after an overnight fast of at least 10 hours]

Reference Product (Treatment C): Pristiq® 50 mg Extended Release Tablets

Blood samples for desvenlafaxine estimation were taken at the following times, per protocol: prior to drug administration and within one minute of the scheduled time at 1.5, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 18, 24, 36, 48 and 60 hours after dosing hours following drug administration.

Safety Data for Study 2012-2883
There were no deaths or serious adverse events reported during the clinical trial period.

Thirty (30) subjects were enrolled in the study, of which 27 completed the study. Three (3) subjects were removed from therapy/assessment. Subjects 15 and 10 were dismissed in periods 1 and 3 because of the adverse event of vomiting. Subject 27 was dismissed in period 1 because of non-compliance (positive urine COC). There were 50 adverse events involving 18 subjects in the study. All adverse events were judged to be mild in severity.

	Severity			Relation to the Drug		Intervention	
TRT	Mild	Mod	Severe	Reasonable Possibility	No Reasonable Possibility	DT	NDT
A	21	0	0	18	3	0	0
B	14	0	0	7	7	0	2
C	15	0	0	12	3	0	2
Total	50	0	0	37	13	0	4

The majority of adverse events with Treatments A (Teva 50 mg after 10 hour fast), B (Teva 50 mg, 30 minutes after the start of a high fat, high calorie breakfast) and C (Pristiq 50 mg ER) are listed below:

- Treatment A: nausea (n=5), somnolence (n=3), mydriasis (n=2), headache (n=2) and decreased hemoglobin (n=2).
- Treatment B: headache (n=3)
- Treatment C: nausea (n=2), dizziness (n=2), blurred vision (n=2) and increased blood urea (n=2)

Vital signs measurements (blood pressure and pulse rate) were obtained prior to dosing, and at 2, 5, 8 and 10 hours (±20 minutes) post-dose in each period of the study and at study exit. All vital signs were within normal range or not clinically significant (NCS) or returned to normal after repeat measurement.

Conclusion for Study 2012-2883: There appears to be a slight numerical excess of adverse events with Desvenlafaxine Fumarate Extended Release Tablets, 50 mg, when taken on an empty stomach (Treatment A) compared to when taken with high fat foods (Treatment B). In general desvenlafaxine fumarate ER tablet, 50 mg was well tolerated in this study.

Overall Safety Conclusion(s) for Studies 53811, 53711 and 2012-2883: In general desvenlafaxine fumarate ER tablet, 50 and 100 mg were well tolerated in this study. A slight numerical excess of adverse events (nausea, emesis, somnolence) were present when desvenlafaxine fumarate ER tablets were taken on an empty stomach in studies 53711 and 2012-2883. However, given the small numbers of subjects and limited exposures, no definitive conclusions as to ultimate safety differences can be made.

IV. OCP Review

Based on the preliminary reports from OSI (Refer: VIII: Inspection below), the Office of Clinical Pharmacology (OCP) cannot finalize their review. They have asked the sponsor to provide recalculated data to this submission. Based upon their preliminary review they have concluded that: 1) Desvenlafaxine ER tablet is bioequivalent to Pristiq ER at the strengths of 50 mg and 100 mg; 2) Desvenlafaxine fumarate ER can be administered with or without food; and 3) Desvenlafaxine fumarate ER exhibits extended release characteristics similar to the approved Pristiq ER.

The preliminary findings of the clinical pharmacology studies are summarized below.

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

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

[*]Median (range), [#]Arithmetic mean (CV%)

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

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

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

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

V. Pharmacology/Toxicology Review

A review by Drs. Mathew and Fossom concluded that based upon the absence of impurities, degradants, or novel excipients in Desvenlafaxine Fumarate Extended Release tablets, no additional toxicological characterization was required and there were no Pharmacology/ Toxicology issues preventing approval of this NDA.

VI. Patient Labeling Review

Twanda Scales and Nazia Fatima of The Divisions of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed the Medication Guide (MG) and found it to be acceptable with their recommended changes.

VII. Label, Labeling and Packaging Review

Loretta Holmes, Irene Chan and Scott Dallas of Division of Medication Error Prevention and Analysis (DMEPA) provided labeling comments.

VIII. Inspection

The Office of Scientific Investigations (OSI)\ Division of Bioequivalence and GLP Compliance (DBGLPC) conducted an inspection of Bio-Kinetic Clinical Applications LLC from June 25, (b) (4) and made the following observations: Study 5371, an AE on Subject 26 was not reported to the sponsor; inaccurate case histories were maintained for Study 5371 for Subjects 17, 18. Another inspection of (b) (4) identified problems

related to a bioanalytical validation study PMRI-1285-11. These preliminary reports were reviewed as part of this review. OSI final review is still pending at the filing of this review.

IX. Pediatric Plan

Sponsor has requested a Full-Waiver for studies in all pediatric ages. The Division has informed them that we would grant a Partial Waiver only for children age 0-6 years of age with MDD and a Deferral for MDD studies in children (7-11 years old) and adolescents (12-17 years old) as long as we receive a proposal for such studies. At the time of this review, no proposal has been received by DPP. Once the innovator's PREA requirements are met and the innovator's studies have been fully assessed, DPP would then re-evaluate this Partial Waiver and Deferral, and likely issue a Full-Waiver for this 505(b)(2) application.

Pediatric Review Committee (PeRC) Waivers and Deferral templates have been submitted to PERC and will likely be modified once DPP has received and reviewed sponsor's proposals for the above studies.

X. Conclusions and Recommendations

An approval action is recommended pending our receipt and review of the Office of Scientific Investigations (OSI) final consultant report and Office of Clinical Pharmacology (OCP) final review.

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/s/

GLENN B MANNHEIM
09/05/2013

JING ZHANG
09/05/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA No: 205, 208

IND: 113, 629

Applicant: Teva Pharmaceuticals USA

Stamp Date: December 13, 2012

Drug Name: Desvenlafaxine Fumarate Extended-Release Tablets, Eq. to 50 mg & 100 mg base

NDA/BLA Type: 505(b)(2)

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?			X	
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			Pristiq® Extended-Release Tablets, Eq. to 50 mg & 100 mg base, Wyeth Pharm Inc, NDA 021, 992
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? *Pivotal Study #1:* 50 mg Study: 2012-2883: A Single-Dose, Comparative Bioavailability Study of One Formulation of Desvenlafaxine Fumarate Extended Release Tablets, Equivalent to 50 mg Desvenlafaxine and One Formulation of Pristiq® Extended Release Tablets, 50 mg under Fasting and Fed Conditions. • Indication: 50 mg under Fasting and Fed *Pivotal Study #2:* For the 100 mg Fasted Study: 2011-2749 BA/PK (Clinical Study No. 53711): A Pivotal, Open-Label, Single-Center, Randomized, Single-Dose, Two-Period, Two-Treatment, Two-Sequence Crossover Study to Compare the Bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets, Equivalent to 100 mg Desvenlafaxine to Pristiq® Extended-Release Tablets, 100 mg Under Fasted Conditions • Indication: This pivotal study was an open-label, randomized, two-treatment, two-period, two-sequence crossover study to evaluate the relative bioavailability of Teva's Desvenlafaxine Fumarate ER Tablets 100 mg to Wyeth Pharmaceuticals Inc.'s Pristiq® ER Tablets, 100 mg. This study enrolled 34 healthy, adult subjects. *Pivotal Study #3:* 100 mg Fed Study: 2011-2750 BA/PK (Clinical Study No. 53811): A Pivotal, Open-Label, Single-Center, Randomized, Single-Dose, Two-Period, Two-Treatment, Two-Sequence Crossover Study to Compare the Bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets, Equivalent to 100 mg Desvenlafaxine to Pristiq® Extended-Release Tablets, 100 mg Under Fed Conditions • Indication: This pivotal study was an open-label, randomized, two-treatment, two-period, two-sequence crossover study to evaluate the relative bioavailability of Teva's Desvenlafaxine Fumarate ER Tablets 100 mg to Pristiq® ER Tablets, 100 mg. This study enrolled 24 healthy, adult subjects.	X			Study: 2012-2883 is missing synopsis file (2012-2883-synopsis.pdf). All 3 studies do not contain subject narratives.
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			
17.	Has the application submitted a rationale for assuming the			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	applicability of foreign data to U.S. population/practice of medicine in the submission?				
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 arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
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	
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			Needs to propose a study
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.			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).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	population?				
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			On face it appears adequate.
34.	Are all datasets to support the critical safety analyses available and complete?	X			On face it appears adequate.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			On face it appears adequate.
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			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____

The following clinical studies are included with this submission:

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant. Response: N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. Response: Refer to reviewer comments below.

Medical Officer Reviewer Summary Comments: No integrated summaries of safety or efficacy could be identified. Study: 2012-2883 is missing synopsis file (2012-2883-synopsis.pdf). All 3 studies do not contain subject narratives for those who were discontinued from the study. The sponsor will need to propose a pediatric study with the request for a pediatric waiver.

There are no objections to filing of this NDA. A request for the above missing information should be sent to the sponsor.

Team Leader Comments:

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Glenn Mannheim, M.D.	January 31, 2013
Reviewing Medical Officer	Date
Jing Zhang, M.D.	January 31, 2013
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/

GLENN B MANNHEIM
01/31/2013

JING ZHANG
02/01/2013