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APPLICATION NUMBER:

204150Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA, 505(b) (2)
Application Number(s)	N 204150
Priority or Standard	Standard
Submit Date(s)	February 29, 2012
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Filing Meeting	April 23, 2012
PDUFA Goal Date	December 28, 2012
Division / Office	OND I/DPP
Reviewer Name(s)	Glenn Mannheim, M.D.
Review Completion Date	November 27, 2012
Established Name	Desvenlafaxine
(Proposed) Trade Name	Desvenlafaxine (Base) Extended-Release Tablets 50 mg and 100 mg
Therapeutic Class	Antidepressant: selective serotonin and norepinephrine reuptake inhibitor (SNRI)
Applicant	ALEMBIC PHARMACEUTICALS LTD
Formulation(s)	Extended-Release Tablets
Dosing Regimen	50 mg and 100 mg
Indication(s)	Major Depressive Disorder
Intended Population(s)	Major Depressive Disorder (Adults)

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 113100, Ranbaxy Laboratories met with FDA on October 5, 2011 to discuss a proposed 505(b) (2) application for Desvenlafaxine (Base) Extended-Release Tablets 50 mg and 100 mg using Pristiq as the reference listed drug. Two proposed pharmacokinetic studies (50 mg and 100 mg) including food effect on 100 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. A May Proceed Letter was issued by FDA on December 14, 2011. NDA 204150 was submitted on February 28, 2012 and contains a Letter for Authorization for Alembic Pharmaceuticals Ltd to reference IND 113100 and submit this NDA (\\Cdsesub1\evsprod\NDA204150). Both studies were done in India.

II. Materials Reviewed

Bioequivalence Studies 413-11 (*Fasting and Food Study*) and 455-11(*Fasting Study*)
Desvenlafaxine Clinical Literature
Proposed Labeling
Case Report Forms
Financial Disclosure Certification
Debarment Certification

III. Review of Clinical Safety Data

Study 413-11 : 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.

This study was conducted to assess the bioequivalence of desvenlafaxine (Base) Extended-Release Tablets 100 mg to the Reference Product [PRISTIQ® (desvenlafaxine) Extended-Release Tablets 100 mg] after single oral dose to healthy, adult, human subjects under fasting condition. Similarly, food effect was evaluated by comparing relative bioavailability of desvenlafaxine (Base) Extended-Release Tablets 100 mg in healthy, adult, human subjects under Fasting and 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, the subjects were administered a single oral dose of either the test or the reference product with 240 mL of drinking water

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Single dose of the test or the reference product was administered orally to each subject in Period-I, Period-II and Period-III. A washout period of 7 days was maintained between the two dosing periods.

Treatment sequence

Sequence	Period-I	Period-II	Period-III
1	Treatment-T2 (Test)	Treatment-R (Reference)	Treatment-T1 (Test)
2	Treatment-T1 (Test)	Treatment-T2 (Test)	Treatment-R (Reference)
3	Treatment-R (Reference)	Treatment-T1 (Test)	Treatment-T2 (Test)

Blood samples for desvenlafaxine estimation were taken at the following times, per protocol: pre-dose, at 1.0, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 10.0, 11.0, 12.0, 16.0, 20.0, 24.0, 30.0, 36.0, 48.0 and 72.0 hours post-dose, a total of 24 samples.

Safety Data for Study 413-11

A total of 50 subjects were enrolled with 35 completing the study.

No deaths or serious AEs were reported during the course of the study. Seven subjects are identified (Appendix No. 16.2.1) as having discontinued from the study. The reasons were nausea (n=4), vomiting (n=4), dizziness (n=1), loose stools (n=1) and fever (n=1). All were excluded from the efficacy analysis. CRF's on two of these subjects are provided (Subject's 1001 and 1039 who withdrew because of fever and nausea; and loose stools).

Twenty two adverse events (AEs) were reported by sixteen subjects during the conduct of the study. Eight AEs were reported in Period-I, seven in Period-II, six in Period-III and one in the post-study. Seven AEs were reported after receipt of the Reference Product-R, ten after receipt of the Test Product-T1 and five after receipt of the Test Product-T2. All the AEs were described by the sponsor as being mild in nature with subjects being followed until resolution. The causality assessment by the sponsor was judged as possible for 19 AEs, as unlikely for three.

Conclusion for Study 413-11: Vomiting (3/50, 6 %) and nausea (6/50, 12 %) were more common as adverse events in the Test Product than the Reference Drug (vomiting 1/50: 2 %; nausea 1/50: 2 %) in this study. Comparison with Common Adverse Reactions (Table 3) of Pristiq's PLR 100 mg dose showed that vomiting and nausea were comparable with the Pristiq (vomiting: 4% vs.

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6%; nausea: 26% vs. 12% (%). Vomiting (3/50, 6 %) and nausea (3/50, 6 %) were the most commonly associated with study discontinuation.

Study 455-11: This was an open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, oral, crossover bioequivalence study of Desvenlafaxine (base) Extended-Release Tablets 50 mg in healthy, adult human subjects under fasting conditions.

This study was conducted to compare the bioavailability and characterize the pharmacokinetic profile of desvenlafaxine (Base) extended-release tablets 50 mg relative to that of reference formulation, PRISTIQ® (Desvenlafaxine) Extended-Release Tablets 50 mg made by Wyeth Pharmaceuticals Inc., in healthy, adult, human subjects under fasting conditions and to assess the bioequivalence.

Dose and Mode of Administration

Reference Product-R: Pristiq® (Desvenlafaxine Extended-Release Tablets 50 mg)

Test Product-T: Desvenlafaxine (Base) Extended-Release Tablets 50 mg

After an overnight fast of at least 10 hours, a single dose of either the test or the reference product was administered orally to each subject in Period-I & Period-II. A washout period of 7 days was maintained between the two dosing periods. Blood samples for desvenlafaxine estimation were taken at the following times, per protocol: pre-dose, at 1.0, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 10.0, 11.0, 12.0, 16.0, 20.0, 24.0, 30.0, 36.0, 48.0 and 72.0 hours post-dose, a total of 24 samples.

Safety Data for Study 455-11

A total of 52 subjects were enrolled with 41 completing the study.

No deaths or serious AEs were reported during the course of the study. Seven adverse events were reported by six subjects (6) during the conduct of the study. Five were reported in Period-I and two in Period-II of the study. Three AEs were reported by 2 subjects after receipt of the Test Product and four AEs were reported by four subjects after receipt of the Reference Product.

Seven subjects are identified (Appendix No. 16.2.1) as having discontinued from the study. The reasons were vomiting (n=5), loose stools (n=4) and alcohol consumption (n=1). Seven of these subjects were excluded from the efficacy analysis. CRF's are provided for Subject 1030 who developed 3-4 episodes of watery loose stools.

Conclusion for Study 455-11: Vomiting and diarrhea/loose stools occurred in both Test Product and Reference Drug. No meaningful differences were apparent.

Overall Safety Conclusion(s) for Studies 413-11 and 455-11: Vomiting and nausea seem to be more common as adverse events in the 100 mg Test Product than the 100 mg Reference Drug. No meaningful differences could be identified in the 50 mg Test Product compared to the 50 mg Reference Drug. Loose stools seem to be less in Study 413-11 than in study 455-11 which may

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be related to the presence of food for Study 413-11. It is possible the base formulation may be more of a gastric irritant at the 100 mg dose. However, given the small numbers of subjects and limited exposures, no definitive conclusions as to ultimate differences in safety can be made.

IV. OCP Review

The review team in the Office of Clinical Pharmacology (OCP) (refer to the review of Kofi Kumu, Ph.D.) recommends an approval of Desvenlafaxine Extended Release (ER) tablets at the same dosing recommendation approved for Pristiq for the treatment of major depressive disorder (MDD) in adults. Desvenlafaxine (Base) 50 and 100 mg Extended-Release Tablets were compared to Pristiq (Desvenlafaxine) 50 and 100 mg Extended-Release Tablets, and found to be bioequivalent to the Pristiq (Desvenlafaxine) 50 and 100 mg Extended-Release Tablets, and that it could be administered with and without food.

The findings of the clinical pharmacology study are summarized below. Statistical results for the comparison of the desvenlafaxine ER 50 mg and 100 mg tablets to Pristiq are shown in the tables below.

Table 1: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Desvenlafaxine 100 mg under fasting conditions

Parameters	Geometric Least Squares Mean			90% Confidence Interval
	Desvenlafaxine ER (Test- T)	Pristig (Reference-R)	Ratio (T/R) (%)	
C _{max} (ng/mL)	282.75	252.75	111.9	105.5 – 118.6
AUC _(0-t) (ng*h/mL)	6392.62	5869.84	108.9	100.4 – 118.2
AUC _(0-∞) (ng*h/mL)	6468.06	5937.48	108.9	100.5 – 118.1

Table 2: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Desvenlafaxine 50 mg under fasting conditions

Parameters	Geometric Least Squares Mean			90% Confidence Interval
	Desvenlafaxine ER (Test)	Pristig (Reference)	Ratio (T/R) (%)	
C _{max} (ng/mL)	121.41	117.47	103.4	95.08 – 112.35
AUC _(0-t) (ng*h/mL)	2729.88	2503.69	109.0	98.09 -121.20
AUC _(0-∞) (ng*h/mL)	2778.84	2544.24	109.2	98.36 – 121.28

Administration of Desvenlafaxine ER with a high fat meal (800 – 1000 calories) did not have a significant effect on the extent of absorption (AUC) but an increase of 23% in peak concentration (C_{max}) was observed. This was thought not to be clinically significant.

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V. Inspection

The Office of Scientific Investigations (OSI)\ Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and bioanalytical portions of bioequivalence studies 413-11 and 455-11 at (b) (4) and determined them to be acceptable (Refer to October 09, 2012 Review).

VI. Chemistry, Manufacturing and Controls (CMC)

CMC issued a deficiency letter dated August 07, 2012 (refer to Information Request Letter of Ramesh Sood). The applicant addressed all the identified CMC deficiencies, and CMC has recommended that this NDA for desvenlafaxine extended-release tablets (50 mg and 100 mg) be approved (Refer to November 26, 2012 Review).

VII. Division of Medication Error Prevention and Analysis (DMEPA)

The Division of Medication Error Prevention and Analysis reviewed the proposed container labels, carton and insert labeling for Desvenlafaxine (Base) Extended-release Tablets for areas of vulnerability that could lead to medication errors and made various recommendations (refer to November 04, 2012, Review of Loretta Holmes, BSN, PhamD).

VIII. Pediatric Plan

At Pristiq approval on Jan. 22, 2007, FDA requested the innovator to conduct children and adolescent (7-17 years old) MDD studies to assess the safety and efficacy of desvenlafaxine in these population as a PREA requirement. These studies currently are on going. Based upon this, a request to defer children and adolescent MDD studies with desvenlafaxine (base) has been made by the Division until the innovator completes their pediatric studies. PerRC met with the Division on Nov. 14, 2012 and agreed with the Division's requests.

A full waiver for doing pediatric studies in children less than 7 years was requested by the Division and granted at the PerRC meeting held on November 14, 2012. This was based upon difficulties in ascertainment and recruitment of children with major depressive disorder in these age groups.

IX. Conclusions and Recommendations

An approval action is recommended pending agreement on the final labeling.

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/s/

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11/28/2012

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