CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204150Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA:	204150
Generic Name:	Desvenlafaxine (base)
Trade Name:	TBD
Strength and Dosage Form:	50 mg and 100 mg Extended Release Tablets
Indication:	Major Depressive Disorder (MDD)
Sponsor:	Alembic Pharmaceuticals
Submission Type:	Original NDA [505(b)(2)]
Priority Classification:	Standard
Submission Date:	2/29/12
OCP Division:	DCP1
OND Division:	DPP
Reviewer:	Kofi Kumi, Ph.D.
Team Leader:	Hao Zhu, Ph.D.

Table of Content

1. Executive Summary

The sponsor submitted Desvenlafaxine (base) Extended Release (ER) tablets as a 505(b)(2) application using Pristiq® as the reference product. The development program mainly depended on demonstrating bioequivalence between Desvenlafaxine (base) ER and Pristiq. Clinical safety and efficacy studies were not conducted for this application. The sponsor is seeking the indication of major depressive disorder which is approved for Pristiq. Our findings are summarized as follows:

- Desvenlafaxine (base) ER is bioequivalent to Pristiq, at the strengths of 50 mg and 100 mg, under fasting conditions.
- Desvenlafaxine (base) ER can be administered with or without food.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) supports a recommendation for approval of Desvenlafaxine (base) ER (Alembic Pharmaceuticals) at the same dosing recommendation approved for Pristiq for the treatment of major depressive disorder (MDD).

1.2 Post-Marketing Studies

No post-marketing studies are recommended by OCP.

1.3 Labeling Recommendations

The following language should be incorporated into the label under Pharmacokinetics, Section 12.3

The mean terminal half-life, $t_{1/2}$, after administration of Desvenlafaxine ER is approximately 9.2 ± 1.3 hours. The median (range) time to peak concentration (Tmax) was 6 (3 – 24) hours after administration of 50 mg Desvenlafaxine ER.

A food-effect study involving administration of Desvenlafaxine ER to healthy subjects under fasting and fed conditions (800 – 1000 calories) indicated that the C_{max} was increased about 23% in the fed state, while the AUCs were similar. This difference in Cmax is not expected to be clinically significant; therefore, Desvenlafaxine ER can be taken without regard to meals.

The following recommendation should be added to the label in Section 7, Drug Interaction Drugs metabolized by CYP2D6 (desipramine)

Concomitant use of 400 mg Desvenlafaxine with a drug metabolized by CYP2D6 (e.g. desipramine, dextromethorphan, metoprolol, atomoxetine resulted in higher concentrations of desipramine. Reduce the doses of CYP2D6 substrates (e.g. desipramine) by one-half when coadministered with 400 mg Desvenlafaxine ER. CYP2D6 substrates should be dosed at the original level when Desvenlafaxine is discontinued or the dose of Desvenlafaxine is reduced to 100 mg or below (see Section 12.3).

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Bioequivalence
Desvenlafaxine (base) 50 mg and 100 mg ER are bioequivalent to Pristiq® (Desvenlafaxine succinate) 50 mg and 100 mg ER Tablets, respectively, under fasting conditions. The following are the statistical results (Table 1 and Table 2) for the comparison of Desvenlafaxine ER 100 mg and 50 mg tablets to Pristiq.

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) (%)	
Cmax (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
$AUC_{(0-\infty)}$ (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

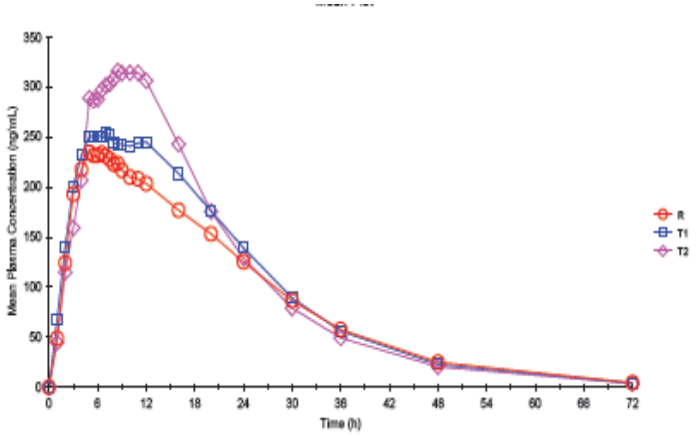
Parameters	Geometric Least Squares Mean			90% Confidence Interval
	Desvenlafaxine ER (Test)	Pristig (Reference)	Ratio (T/R) (%)	
Cmax (ng/mL)	121.41	117.47	103.4	95.08 – 112.35
$AUC_{(0-t)}$ (ng*h/mL)	2729.88	2503.69	109.0	98.09 -121.20
$AUC_{(0-\infty)}$ (ng*h/mL)	2778.84	2544.24	109.2	98.36 – 121.28

The Tmax of desvenlafaxine after administration of Desvenlafaxine (base) ER and Pristiq are comparable. Median (range) Tmax for the recommended dose, 50 mg, after administration of Desvenvenlafaxine (base) ER and Pristiq were 6.0 (3.0 – 24.0) and 5.5 (2.0 – 20.0) hours, respectively. After administration of Desvenlafaxine (base) ER and Pristiq 100 mg, the median (range) time to peak concentration (Tmax) for desvenlafaxine were 9.0 (3.0 – 24.0) and 5.5 (3.0 – 16.0) hours, respectively. The difference in median Tmax after 100 mg dose is not expected to be clinically relevant, given the nature of the indication (major depressive disorder).

Effect of food
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 (Cmax) was observed. The increase in peak concentration was statistically significant. Cmax of Pristiq was increased by about 16% when it was given with food and Pristiq is recommended to be given with or without food. The additional 7% increase in Cmax of desvenlafaxine seen after administration of Desvenlafaxine ER with food, assuming not due to cross-trial variability, is not expected to be clinically meaningful.Therefore, Desvenlafaxine ER tablets can also be given with or without food. Median (range) Tmax after administration of Desvenlafaxine (base) ER under fed and fasting conditions were 8.5 (3 – 16) and 9.0 (3.0 – 24) hours, respectively . The following

graph (Figure 1) depicts the plasma concentration time profile for Desvenlafaxine ER compared to Pristiq 100 mg under fasting conditions and the effect of food (800- 1000 calories) on Desvenlafaxine ER.

Figure 1: Plasma concentration time profile after administration Desvenlafaxine ER tablets and Pristiq



R= Pristiq fasting, T1- Desvenlafaxine ER – fasting , T2- Desvenlafaxine ER- Fed

Alcohol Dose Dumping
Dose dumping due to alcohol was not observed based on an *in vitro* study. Refer to biophmarmaceutics review.

Clinical and Bioanalytical Site Inspections:
The bioequivalence studies were inspected by the Office of Scientific Investigations (OSI) and found the clinical and bioanalytical portions to be acceptable (Refer to the OSI inspection review in the Appendix (4.2)).

2. Question Based Review (QBR)

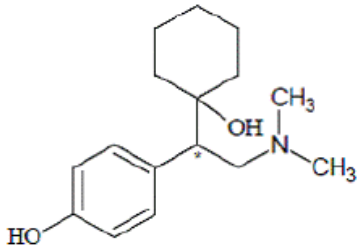
2.1 General Attributes

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

The sponsor submitted a 505(b)(2) applications for Desvenlafaxine ER tablets. The reference drug for this application is Pristiq® (desvenlafaxine succinate) ER tablet which is currently approved for the treatment of major depressive disorder (MDD). The application was mainly based on demonstration of bioequivalence between Desvenlafaxine ER and Pristiq. Clinical safety and efficacy studies were not conducted.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics?

Desvenlafaxine is a white to off-white crystalline powder that is sparingly soluble in dimethyl sulfoxide. The following is the structure of desvenlafaxine (Figure 2).



* Chiral Centre

Fig 2: Structure of Desvenlafaxine

Desvenlafaxine (O-Desmethyl Venlafaxine) structure contains one chiral carbon atom in its structure and exists as (+) and (-) enantiomers. The sponsor has developed an ER tablet formulation that contains desvenlafaxine (base) as the active moiety. The reference product, Pristiq, contains desvenlafaxine succinate as the active moiety.

2.1.3. What are the proposed mechanism (s) of action and therapeutic indication(s)?

Desvenlafaxine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). It is indicated for the treatment of major depressive disorder (MDD).

2.1.4. What are the proposed dosage and route of administration?

The recommended dose for desvenlafaxine is 50 mg daily, with or without food administered orally. In clinical studies doses of 50 to 400 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg/day and adverse events and discontinuations were more frequent at higher doses.

2.1.5. What is the reported adverse event profile from the bioequivalence studies?

The sponsor reported that in general, the clinical portion of the bioequivalence studies were completed with no serious adverse event (AE). The investigational drugs were well tolerated by healthy subjects, as a single dose administration. There were no deaths or serious adverse event reported in the study. The sponsor reported two significant AEs were reported in two subjects during the course of the study 455-11. Diarrhea to Subject No. 1030 in Period-I and Diarrhea to Subject No. 1028 in Period-II. These subjects were not on the investigational product. Both subjects were withdrawn from the trial on medical grounds and were treated accordingly. The subjects were followed up for their AEs until resolution. The sponsor reported that there were no clinically significant findings in the vital signs assessment or the laboratory tests for any of the subjects.
Refer to medical review for Agency's assessment of safety.

2.2. General Clinical Pharmacology and Biopharmaceutics

2.2.1 What are the design features of the clinical pharmacology and/or bopharmaceutics studies used to support dosing or claims?

The sponsor is seeking approval for treatment of major depressive disorder (MDD) which is currently approved for Pristiq. Therefore, the following bioequivalence studies comparing Desvenlafaxine ER (desvenlafaxine base) to Pristiq (desvenlafaxine succinate) are the basis for dosing and claims.

1. Study 413-11 was an open label, balanced, randomized, two-treatment, three-period, three sequence, single oral dose, crossover study to evaluate bioequivalence of Desvenlafaxine ER Tablets 100 mg with Pristiq ER 100 mg as reference under fasting conditions and evaluation of food effect by relative bioavailability of Desvenlafaxine ER Tablets 100 mg under fasting and fed conditions in healthy adult human subjects.

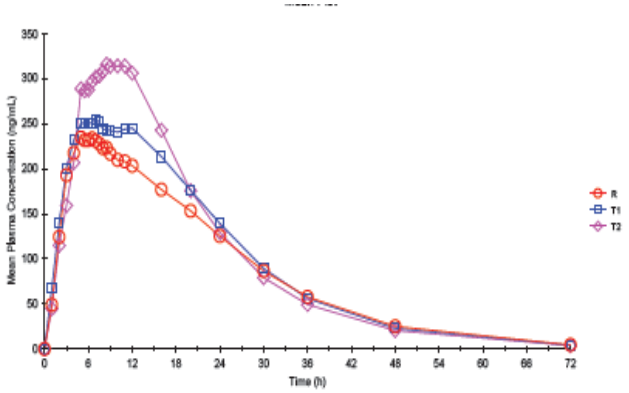
2. Study 455-11 was an open label, balanced, randomized, two-treatment, two-period, two sequence, single dose, oral, crossover bioequivalence study of Desvenlafaxine ER tablets 50 mg with Pristiq 50 mg as reference in healthy, adult human subjects under fasting conditions.

2.2.2. Is Desvenlafaxine (base) 100 mg ER bioequivalent to the reference listed drug, Pristiq (desvenlafaxine succinate) 100 mg ER?

Desvenlafaxine 100 mg ER tablets (Alembic Pharmaceuticals) and Pristiq® (desvenlafaxine succinate) 100 mg ER tablets (Wyeth) are bioequivalent under fasting conditions.

The sponsor conducted an open label, balanced, randomized, two-treatment, three period, three sequence, single oral dose, crossover study to evaluate bioequivalence of Desvenlafaxine (base) ER tablets 100 mg under fasting conditions in healthy adult human subjects under fasting conditions. Figure 3 contains the mean plasma concentration of desvenlafaxine versus time curves after administration of Pristiq (R) and Desvenlafaxine ER under fasting (T1) and fed (T2) conditions.

Figure 3: Plasma concentration time profile after administration Desvenlafaxine ER tablets and Pristiq



R= Pristiq fasting, T1- Desvenlafaxine ER – fasting , T2- Desvenlafaxine ER- Fed

The disposition of desvenlafaxine was similar after administration under fasting conditions of Desvenlafaxine ER and Prisiq.

Table 3 contains the statistical results of the study including the 90% confidence interval.

Table 3: 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) (%)	
Cmax (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
$AUC_{(0-\infty)}$ (ng*h/mL)	6468.06	5937.48	108.9	100.5 – 118.1

These results were similar to that obtained by the reviewers when they recalculated the 90% confidence intervals. And the results meet the regulatory criteria for declaring two products to be bioequivalent.

2.2.4 Is the exposure to Desvenlafaxine significantly different after administration of Desvenlafaxine (base) ER 100 mg was administered with or without food?

Administration with a high fat meal did not have a significant effect on the extent of absorption (AUC) but an increase of 23% in peak concentration (Cmax) was observed. The increase in peak concentration was statistically significant but is not expected to be clinically relevant. Cmax for Pristiq was increased by about 16% when it was given with food and Pristiq is recommended to be given with or without food. The additional 7% increase in Cmax of desvenlafaxine seen after administration of Desvenlafaxine ER with food, assuming not due to cross-trial variability, is not expected to be clinically meaningful. Therefore, Desvenlafaxine ER tablets (Alembic Pharmaceuticals) can also be given with or without food.

An open label balanced randomized two-treatment, three period, three sequence, single oral dose, crossover study to evaluate bioequivalence of Desvenlafaxine (base) ER tablets 100 mg under fasting conditions and evaluation of food effect by relative bioavailability of Desvenlafaxine (base) ER tablets 100 mg under fasting and fed conditions in healthy adult subjects. Table 4 contains the results of the statistical analysis evaluating the effect of a high fat meal.

Table 4: Geometric Least Squares Mean, (Fed/Fasting) Ratios, and 90% Confidence Interval for Desvenlafaxine ER 100 mg Under Fasting and Fed Conditions

Parameters	Geometric Least Squares Mean			90% Confidence Interval
	Desvenlafaxine ER (Fasting)	Desvenlafaxine ER (Fed)	Ratio (Fed/Fasting) (%)	
Cmax (ng/mL)	282.75	348.93	123.4	116.4 – 130.8
$AUC_{(0-t)}$ (ng*h/mL)	6392.62	6883.75	107.7	99.2 – 116.9
$AUC_{(0-\infty)}$ (ng*h/mL)	6468.06	6938.01	107.3	98.9 -116.3

2.2.5 Is Desvenlafaxine (base) 50 mg ER bioequivalent to the reference listed drug, Pristiq (desvenlafaxine succinate) 50 mg ER?

Desvenlafaxine (base) ER tablets 50 mg (Alembic) and Pristiq® ER Tablets 50 mg are bioequivalent.

The study was a single dose, open label, balanced, randomized, two-treatment, two-period, two-sequence, oral, crossover study of Desvenlafaxine (base) 50 mg ER compared to Pristiq (Desvenlafaxine succinate) 50 ER tablets in healthy adults. Figure 4 contains the mean plasma concentration time profile for desvenlafaxine after administration of Desvenlafaxine ER and Pristiq 50 mg.

Figure 4: Mean plasma concentration time profile

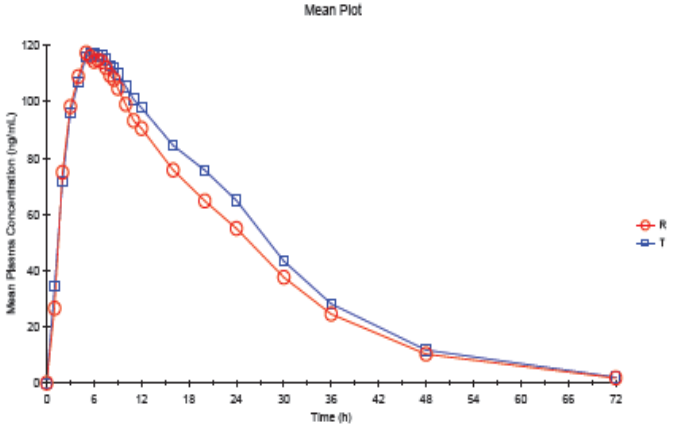


Table 5 contains the results of the statistical analysis for the study.

Table 5: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Desvenlafaxine 50 mg

Parameters	Geometric Least Squares Mean			90% Confidence Interval
	Desvenlafaxine ER (Test)	Pristig (Reference)	Ratio (T/R) (%)	
Cmax (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
$AUC_{(0-\infty)}$ (ng*h/mL)	2778.84	2544.24	109.2	98.36 – 121.28

These results were similar to that obtained when the reviewers recalculated the 90% confidence interval. And they met the regulatory criteria for declaring two products to be bioequivalent.

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

After administration of Desvenlafaxine (base) 50 mg ER by Alembic Pharmaceuticals, the mean elimination half-life (T ½) was 9.1 ± 1.3 hours which is similar to that observed after administration of Pristiq. The median (range) time to peak concentration (Tmax) was 6.0 (3 – 24) hours.

Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. Approximately 45% of desvenlafaxine is excreted unchanged in urine at 72 hours after oral administration. Approximately 19% of the administered dose is excreted as the glucuronide metabolite and <5% as the oxidative metabolite (N,O-didesmethylvenlafaxine) in urine.

Refer to Pristiq label for additional Pharmacokinetic information.

2.2.7. What is the composition of Desvenlafaxine base ER formulations used in the bioequivalence studies?

Table 6 contains the qualitative and quantitative composition of Desvenlafaxine (base) ER tablets used in the registration studies.

Table 6: Composition of Desvenlafaxine (Base) ER Tablets 50 mg and 100 mg

Ingredient	Amount (mg) / Tablet		Amount (%) / Tablet		Pharmaceutical Function
	50 mg	100 mg	50 mg	100 mg	
(b) (4)					
Desvenlafaxine (O-Desmethyl Venlafaxine) IH	50.00	100.00			(b) (4)
Alginic Acid (b) (4) NF					(b) (4)
Citric Acid Monohydrate Powder (b) (4) USP					(b) (4)
Hypromellose (b) (4)					(b) (4)
(b) (4) USP					
Microcrystalline Cellulose (b) (4) NF					(b) (4)
(b) (4)					
Povidone (b) (4) USP					(b) (4)
(b) (4) USP *					
(b) (4)					
Hypromellose (b) (4)					(b) (4)
(b) (4) USP					
Talc USP					
Magnesium Stearate NF					
(b) (4)		(b) (4)	-	-	
(b) (4)					
					(b) (4)
Total Weight	**360.50**	**360.50**	**100.00**	**100.00**	

Remarks:

(b) (4)

3. Analytical Methods

3.1. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes, the active moiety, desvenlafaxine was appropriately measured in biological fluids.

3.2. What bioanalytical methods are used to assess concentrations of desvenlafaxine and is the validation complete and acceptable?

The concentrations of desvenlafaxine in human plasma were determined using a precise and accurate LC-MS/MS method. The method was adequately validated and acceptable.

The range of precision and accuracy of the back calculated concentrations of the calibration curve standard points during the study were 1% to 2.8% and 98.6% to 101.2%, respectively. The inter-day precision and accuracy of quality control samples during the study range from 1.9% to 4% and 98.5% to 104.7%, respectively.

4. Appendix

4.1 Individual Studies

Clinical Pharmacology Review

Biopharmaceutics- Bioequivalence

Biopharmaceutics- Bioavailability

Report # 413-11	**Study Period**: 1/11/2012 to 1/29/2012	EDR Link: \\Cdsesub1\evsprod\nda204150\0000\m5\53-clin-stud-rep
Title	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 subjects	
Objectives	To assess the bioequivalence of Desvenlafaxine (base) extended release tablets 100 mg by comparing sponsor's test product relative to that of reference product after single oral dose to healthy, adult, human subjects under fasting conditions To assess food effect by comparing relative bioavailability of Desvenlafaxine (base) extended release tablets 100 mg in healthy, adult, human subjects under fasting and fed conditions	
Study Design		
☑ Bioequivalence	☑ Bioavailability	
Single-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy Vonuteers		
Screening: ≤ 28 days	**Washout:** ≥ 7 days, outpatient	
Period 1/2	Inpatient stay ☑Y ☐ N:	

Treatments: (Active Ingredient: Desvenlafaxine)

	Test	**Reference**
Dosage Form	Tablet	Tablet
Dosage Strength	100 mg	100 mg
Batch #.	IV25001BD	E82707
Administration	Oral	Oral

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)

Sampling Times (PK, plasma)

- Test: 0, 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 16, 20, 24, 30, 36, 48, 72 hours post dose
- Reference: 0, 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 16, 20, 24, 30, 36, 48, 72 hours post dose

Analytical Method: The performance of the analytical method is acceptable. Yes ☑ No ☐
LC/MS/MS. The range of precision and accuracy of the back calculated concentrations of the calibration curve standard points during the study were 1.4% to 2.8% and 99.3% to 101.2%, respectively. The inter-day precision and accuracy of quality control samples during the study range from 2.6 % to 4% and 99% to 104.7%, respectively.

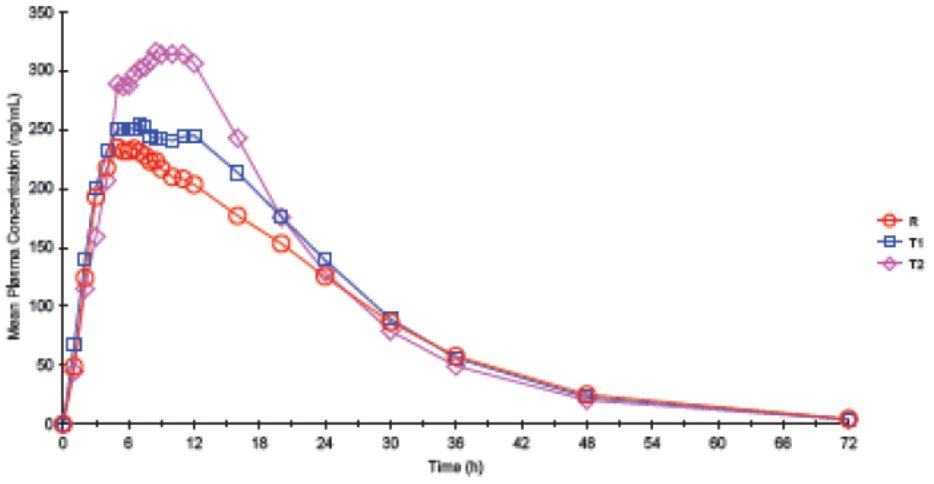
Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	42/35/3 (emesis)
Age [Median (range)]	29.8 ± 4.72 years
Male/Female	32/10
Race (Caucasian/Black/Asian/other)	

Results

Mean Plasma Concentration versus Time Curves after administration Reference (Pristiq) and Test under fasting (T1) and Fed (T2) conditions



Descriptive Statistics for Desvenlafaxine
(n=35)

Parameters (Units)	Mean ± SD (Un-transformed data)		
	Test Product-T		Reference Product-R
	Test Product-T1 (under fast condition)	Test Product-T2 (under fed condition)	
T_{max} (h)*	9.017 (3.017-24.000)	8.500 (3.000-16.000)	5.500 (3.000-16.000)
C_{max} (ng / mL)	289.291±60.4948	355.345±62.6520	256.418±46.2766
AUC_{0-t} (ng.h / mL)	6715.459±1958.5119	7067.924±1535.8421	6135.387±1727.7570
$AUC_{0-\infty}$ (ng.h / mL)	6795.151±1987.5085	7124.841±1558.7786	6207.734±1757.9851
λ_z (1 / h)	0.076±0.0108	0.076±0.0108	0.074±0.0108
$t_{½}$ (h)	9.296±1.3020	9.316±1.2594	9.510±1.3442

T1: Desvenlafaxine ER 100 mg (Fasting), T2: Desvenlafaxine ER 100 mg (fed), R: Pristig 100 mg ER (Fasting)

Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Desvenlafaxine under fasting conditions

Parameters	Geometric Least Squares Mean		Ratio (T/R) (%)	90% Confidence Interval
	Desvenlafaxine ER (Test- T)	Pristig (Reference-R)		
Cmax (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
$AUC_{(0-\infty)}$ (ng*h/mL)	6468.06	5937.48	108.9	100.5 – 118.1

Geometric Least Squares Mean, (Fed/Fasting) Ratios, and 90% Confidence Interval for Desvenlafaxine ER Under Fasting and Fed Conditions

Parameters	Geometric Least Squares Mean		Ratio (T2/T1) (%)	90% Confidence Interval
	Desvenlafaxine ER (Fasting-T1)	Desvenlafaxine ER (Fed –T2)		
Cmax (ng/mL)	282.75	348.93	123.4	116.4 – 130.8
$AUC_{(0-t)}$ (ng*h/mL)	6392.62	6883.75	107.7	99.23 – 116.9
$AUC_{(0-\infty)}$ (ng*h/mL)	6468.06	6938.01	107.3	98.9 -116.3

Site Inspected

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

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
Seven (07) AEs were reported in subject after receipt of the Reference Product-R, Ten (10) AEs were reported in subject after receipt of the Test Product-T1 and Five (05)

AEs were reported in subjects after receipt of the Test Product-T2. All the AEs were mild in nature and the subjects were followed up until resolution. The sponsor reported that the most frequently reported AEs for both treatment groups was nausea. The most reported for the reference (Pristiq) was loose motion.
Conclusion
Desvenlafaxine (base) 100 mg Extended-Release Tablets (Alembic Pharmaceuticals) when Compared with PRISTIQ® (Desvenlafaxine) 100 mg Extended-Release Tablets (Wyeth) meets the bioequivalence criteria with respect to the rate and extent of absorption of Desvenlafaxine under fasting condition. Based on the results obtained, no food effect was observed for the extent of absorption (AUC0-t and AUC0-∞) as it meets the acceptance criteria set in the protocol. A food effect was observed for Desvenlafaxine with respect to the rate of absorption (Cmax), wherein 90% confidence interval for the ratio of Test Product-T2 (Fed) and Test Product-T1 (Fasting), does not fall within the acceptance range of 80.00% - 125.00%. The sponsor states this food effect is consistent with that observed with Pristiq, the reference listed product.
Comments
The reviewer agrees with the sponsor's conclusion. The 23% increase in Cmax after administration of a high fat meal should not be clinically significant. Therefore, Desvenlafaxine ER can be taken with or without food consistent with the innovator product, Pristiq.

Biopharmaceutics- Bioequivalence

Report # 455-11	**Study Period**: 1/16/2012 to 1/23/2012	EDR Link: \\Cdsesub1\evsprod\nda204150\0000\m5\53-clin-stud-rep
Title	An open label balanced randomized two treatment two period two sequence single dose oral crossover bioequivalence study of desvenlafxine (base) extended release tablets 50 mg in healthy adult human subjects under fasting conditions	
Objective	To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's desvenlafaxine (b) (4) extended-release tablets 50 mg relative to that of reference formulation (Pristq) extended release tablets 50 mg in healthy adult human subjects under fasting conditions and to assess the bioequivalence	
Study Design		
☑ Bioequivalence	☐Bioavailability	
Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers		
Screening: ≤ 28 days	**Washout:** ≥ 7 days, outpatient	
Period 1/2	Inpatient stay ☑Y ☐ N:	

Treatments: (Active Ingredient: desvenlafaxine)

	Test	Reference
Dosage Form	Desvenlafaxine Base (Alembic)	Pristiq
Dosage Strength	50 mg	50 mg
Batch #.	IV24003BD	F32683
Administration	Oral	Oral

Sampling Times (PK, plasma)

- Test : 0, 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 16, 20, 24, 30, 36, 48, 72 hours post dose

- Reference: 0, 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 16, 20, 24, 30, 36, 48, 72 hours post dose

Analytical Method: The performance of the analytical method is acceptable. Yes ☑ No ☐
LC/MS/MS. The range of precision and accuracy of the back-calculated concentrations of the calibration curve standard points during the study were 1% to 2.5% and 98.6% to 101%, respectively. The inter-day precision and accuracy of quality control samples during the study 1.9% to 3.8% and 98.5% to 103.7%, respectively.

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

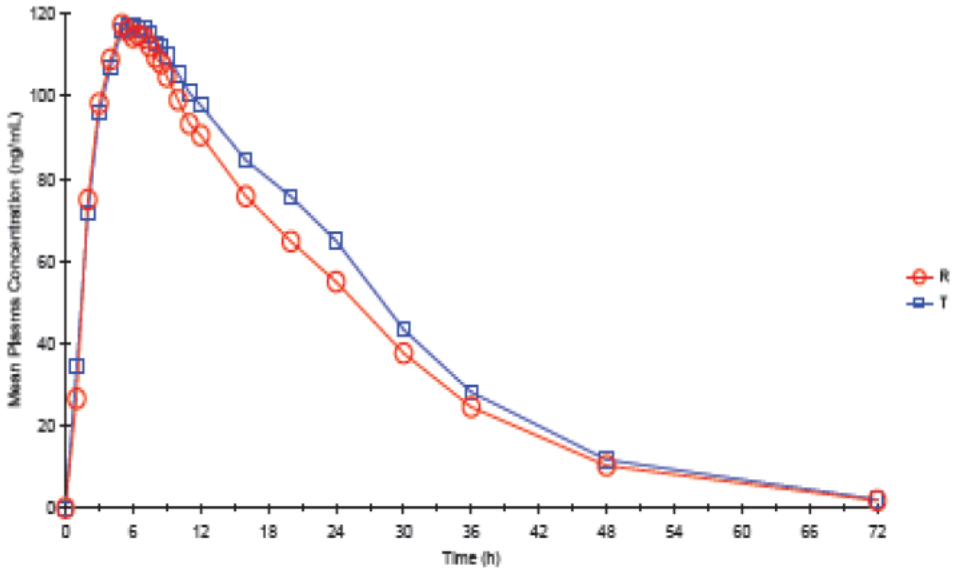
Study Population :

Randomized/Completed/ Discontinued Due to AE	48/41/3
Age [Mean (±SD)]	30.8 ± 4.82
Male/Female	24/24
Race (Caucasian/Black/Asian/other)	

Results

The following figure is the plot of mean plasma concentration of desvenlafaxine versus time after administration of reference (Pristiq 50 mg) and Test (Desvenlafaxine base, 50 mg) products under fasting conditions

Mean Plasma Concentration Time Profile of Desvenlafaxine after administration of Pristiq (R) and Desvenlafaxine base (T)



The following table is the descriptive statistics after administration of Pristiq (R) and Desvenlafaxine base (T).

Descriptive Statistics of Formulation Means for Desvenlafaxine

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	6.000 (3.017-24.000)	5.500 (2.000-20.000)
C_{max} (ng / mL)	126.722±36.2827	123.874±36.2677
AUC_{0-t} (ng.h / mL)	3022.660±1320.9638	2757.652±1037.6249
$AUC_{0-\infty}$ (ng.h / mL)	3073.418±1341.3447	2799.934±1049.5580
λ_z (1 / h)	0.077±0.0114	0.076±0.0121
$t_{½}$ (h)	9.148±1.3484	9.299±1.4193

Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Desvenlafaxine

Parameters	Geometric Least Squares Mean			90% Confidence Interval
	Desvenlafaxine ER (Test- T)	Pristig (Reference-R)	Ratio (T/R) (%)	
Cmax (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
$AUC_{(0-\infty)}$ (ng*h/mL)	2778.84	2544.24	109.2	98.36 – 121.28

Site Inspected

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

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Two significant AEs were reported during the course of the study-Diarrhea in 2 subjects

- (No. 1030 in Period-I and No. 1028 in Period-II). Both the subjects were withdrawn from the trial on medical grounds and were treated accordingly.

Conclusion

Desvenlafaxine (base) Extended-Release Tablets 50 mg (Alembic) when compared with the PRISTIQ® Tablets 50 mg meets the bioequivalence criteria with respect to the rate and extent of absorption of Desvenlafaxine. The subjects were followed up for their AEs until resolution.

Comments

Reviewer agrees with sponsor's conclusion. Desvenlafaxine (base) extended release tablets 50 mg (Alembic) is bioequivalent to the reference listed drug, Pristiq 50 mg ER tablet.

4.2 OSI Inspection Report

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 4, 2012
TO: Thomas P. Laughren M.D.
Director,

Division of Psychiatry Products
FROM: Arindam Dasgupta Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)
THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 204150, Desvenlafaxine (Base) Extended-Release 50 mg and 100 mg Tablets sponsored by ALEMBIC Pharmaceuticals Limited India
At the request of the Division of Psychiatry Products (DPP), the
Division of Bioequivalence and GLP Compliance (DBGLPC) conducted
inspections of the clinical and analytical portions of the following bioequivalence studies:
Study Number-1: 413-11
Study Title: An open label randomized two-treatment three period three sequence single oral dose, crossover study to evaluate bioequivalence of Desvenlafaxine (base) extended release tablets 100 mg [Reference: PRISTIQ® (Desvenlafaxine) Extended-Release Tablets 100 mg, Wyeth Pharmaceuticals Inc., USA.] 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

Study Number-2: 455-11
Study Title: An open label balanced two-treatment two period two sequence single dose oral crossover bioequivalence study of Desvenlafaxine (base) Extended Release Tablets 50 mg [Reference: PRISTIQ® (Desvenlafaxine) Extended-Release Tablets 50 mg, Wyeth Pharmaceuticals Inc., USA.] in healthy adult human subjects under fasting conditions. The audit of the clinical and analytical portions of the studies were conducted at (b) (4) (b) (4) by ORA Investigator Daniel Aisen and OSI Scientist Arindam Dasgupta) and Navi Mumbai, India (conducted 09/24-27/2012 by ORA Investigator Daniel Aisen). The audits included a thorough review of study records, examination of facilities, equipment, interviews and discussions with the firms' management and staff. Following the inspection at the clinical and analytical sites,no objectionable conditions were observed and Form FDA-483s were not issued.

Conclusions:
Following the above inspections, the DBGLPC reviewer recommends that the clinical and bioanalytical portions of studies 413-11 and 415-11 be accepted for further agency review.

Arindam Dasgupta Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classification:
NAI: Clinical Site #1 and Analytical Site (b) (4)

NAI: Clinical Site #2
Lambda Therapeutic Research Ltd., Navi Mumbai, India

FEI: 3006005701
CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Dejernett
DBGLPC/BEB/Haidar/Dasgupta
OND/ODEI/DPP/Laughren/Ansah
OCP/DCP1/Zhu/Kumi
ORA/SE-FO/NOL-DO/NOL-NB/KNOX-TN/Aisen
Draft: AD 10/04/2012
Edit: SHH 10/04/2012
BE File # 6329; O:\BE\EIRCOVER\204150ale.des.doc
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB
FACTS: 1399693
Reference ID: 3199488

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/s/

ARINDAM DASGUPTA
10/09/2012
SAM H HAIDAR
10/09/2012
WILLIAM H TAYLOR
10/09/2012
Reference ID: 3199488

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/s/

KOFI A KUMI
11/29/2012

HAO ZHU
11/29/2012

ONDQA BIOPHARMACEUTICS REVIEW

Original NDA:	**204-150, eCTD-000 and eCDT-0004**
Submission Date:	2/29/2012 and 6/21/2012
Drug Name:	Desvenlafaxine (base) Extended-Release Tablets
Formulation:	Extended-Release Tablets
Strength:	50 and 100 mg
Applicant:	Alembic Pharmaceuticals
Reviewer:	John Duan, Ph.D.
Submission Type:	505(b)(2) NDA

SYNOPSIS

Submission: Original NDA 204-150 for Desvenlafaxine (base) Extended-Release Tablets submitted on 2/29/2012, is being proposed for the treatment of major depressive disorders (MDD). The proposed product contains desvenlafaxine base as the active ingredient compared to Wyeth's RLD product Pristiq® approved under NDA 21-992, which contains desvenlafaxine succinate salt. Bioequivalence studies comparing the proposed and RLD products were conducted for both 50 mg and 100 mg strengths.

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of the in vitro alcohol dose dumping study, the proposed dissolution methodology and acceptance criteria, and the extended release claim.

Reviewer Comments:

1. The results from the in vitro alcohol dose dumping study did not show dose dumping potential for both strengths (50 and 100 mg) of the proposed desvenlafaxine ER product.

2. The following dissolution method and acceptance criteria are acceptable.

Apparatus:	USP I (basket)
Speed:	100 rpm
Medium:	0.9% NaCl in water
Volume:	900 mL

Acceptance criteria:

1h	Between (b) (4) and (b) (4)
4h	Between and
8 h	Between and
20 h	Not less than (b) (4)

3. The extended release claim is acceptable.

RECOMMENDATION

ONDQA-Biopharmaceutics has reviewed the information/data provided in the Original NDA 204-150 for Desvenlafaxine (base) Extended-Release Tablets and found it acceptable. From the Biopharmaceutics perspective, an approval is recommended for this NDA.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Angelica Dorantes, Ph.D. Date
Team Leader
ONDQA Biopharmaceutics

cc: DARRTS/NDA 204-150, R. Lostritto

BIOPHARMACEUTICS EVALUATION

1. Introduction

The Applicant developed an extended-release tablet formulation containing desvenlafaxine base as the active ingredient. It is indicated for the treatment of major depressive disorders (MDD). Bioequivalence studies were conducted for the 50 mg and 100 mg strengths compared to Pristiq (desvenlafaxine succinate salt) 50 and 100 mg strengths, respectively, which was approved under NDA 21-992.

2. The Composition

The compositions of the 50 and 100 mg strengths are shown in the following tables.

Sr. no.	Name of Ingredients	Reference Quality Standards	Quantity (mg.) per Tablet	Ratio (%w/w)
	(b) (4)			
1	Desvenlafaxine (O-Desmethyl Venlafaxine)	IH	50.00	(b) (4)
2	Alginic Acid (b) (4)	NF	(b) (4)	
3	Citric Acid Monohydrate Powder (b) (4)	USP		
4	Hypromellose (b) (4) (b) (4)	USP		
5	Microcrystalline Cellulose (b) (4)	NF		
	(b) (4)			
6	Povidone (b) (4)	USP		(b) (4)
7	(b) (4)	USP		
	(b) (4)			
8	Hypromellose (b) (4) (b) (4)	USP		(b) (4)
9	Talc	USP		
10	Magnesium Stearate	NF		
	(b) (4)			
	(b) (4)			
11	(b) (4)	IH		(b) (4)
12		USP		
Total weight			**360.50**	**100.00**

Sr. no.	Name of Ingredients	Reference Quality Standards	Quantity (mg.) per Tablet	Ratio (%w/w)
[redacted]				
1	Desvenlafaxine (O-Desmethyl Venlafaxine)	IH	100.00	[redacted]
2	Alginic Acid [redacted]	NF	[redacted]	
3	Citric Acid Monohydrate Powder [redacted]	USP		
4	Hypromellose [redacted]	USP		
5	Microcrystalline Cellulose [redacted]	NF		
[redacted]				
6	Povidone [redacted]	USP	[redacted]	
7	[redacted]	USP		
[redacted]				
8	Hypromellose [redacted]	USP	[redacted]	
9	Talc	USP		
10	Magnesium Stearate	NF		
[redacted]				
11	[redacted]			
12				
Total weight			**360.50**	**100.00**

As shown in the above tables, the two strengths are not compositionally proportional. Therefore, the Applicant conducted bioequivalence studies for both strengths and a biowaiver was not requested in this submission

3. Solubility and permeability

Desvenlafaxine base has been recognized as BCS class IV drug substance (i.e. low solubility and low permeability). Being a weakly basic drug, it has good solubility towards acidic pH and poor solubility towards alkaline pH. The Solubility of the drug substance as a function of pH at 37°C is shown below.

The aqueous solubility of desvenlafaxine base at 37°C is low (0.64mg/ml).
[redacted] mg/ml in 0.1N HCl
[redacted] mg/ml in pH 4.5 Acetate [redacted]
[redacted] mg/ml in pH 6.8 phosphate [redacted]

4. QTPP and CQA identification

An analysis of the reference product and its label identified a quality target product profile (QTPP) that included desired release profile. The drug release profile is important for the bioavailability (BA) and bioequivalence (BE) of the product.

Based on the QTPP, the release of the drug was identified as a Critical Quality Attribute (CQA) for use in a risk assessment approach. The criteria for inclusion of CQAs were that these attributes had the potential to be altered by process parameters or formulation variables.

Property		Target	CQA	Justification
Drug Release	Whole tablet	Similar drug release profile as RLD using a predictive dissolution method	Yes	The drug release profile is important for bioavailability (BA) and bioequivalence (BE); therefore, it is critical. Since *in vitro* drug release is a surrogate for *in vivo* performance, a similar drug release profile to the RLD is
	Alcohol-induced dose dumping	Comparable release compared to the RLD in 5%(v/v), 20% (v/v), and 40% (v/v) Alcohol USP in 0.1N HCl dissolution medium		The drug release profile in alcohol is critical to patient safety. The target is set to ensure that alcohol stress conditions do not alter bioavailability of the drug product and introduce additional risks to the patient

Based on this analysis, this review is being focus on the evaluation of the dissolution method and acceptance criteria, and the alcohol dose dumping studies.

5. Dissolution Method Development

Considering therapeutic equivalency with respect to the active moiety, ***desvenlafaxine***; the proposed product was developed with desvenlafaxine base instead of desvenlafaxine succinate, which was used for the RLD product. For product development, the starting dissolution medium was considered as the recommended medium to establish formulation equivalency with the reference product, Pristiq® Extended-Release Tablets. The proposed extended release formulation of desvenlafaxine base was designed to achieve similarity in terms of dissolution and bioequivalence with respect to Pristiq® ER Tablets.

The following tables show the dissolution data of Desvenlafaxine (base) Extended Release Tablets 100 mg (T/2011/003) and 50 mg (T/2011/002), respectively, in 0.9% NaCl in water, 900 ml, USP Apparatus Type I, at 100 and 75 RPM (RPM Change Trials)

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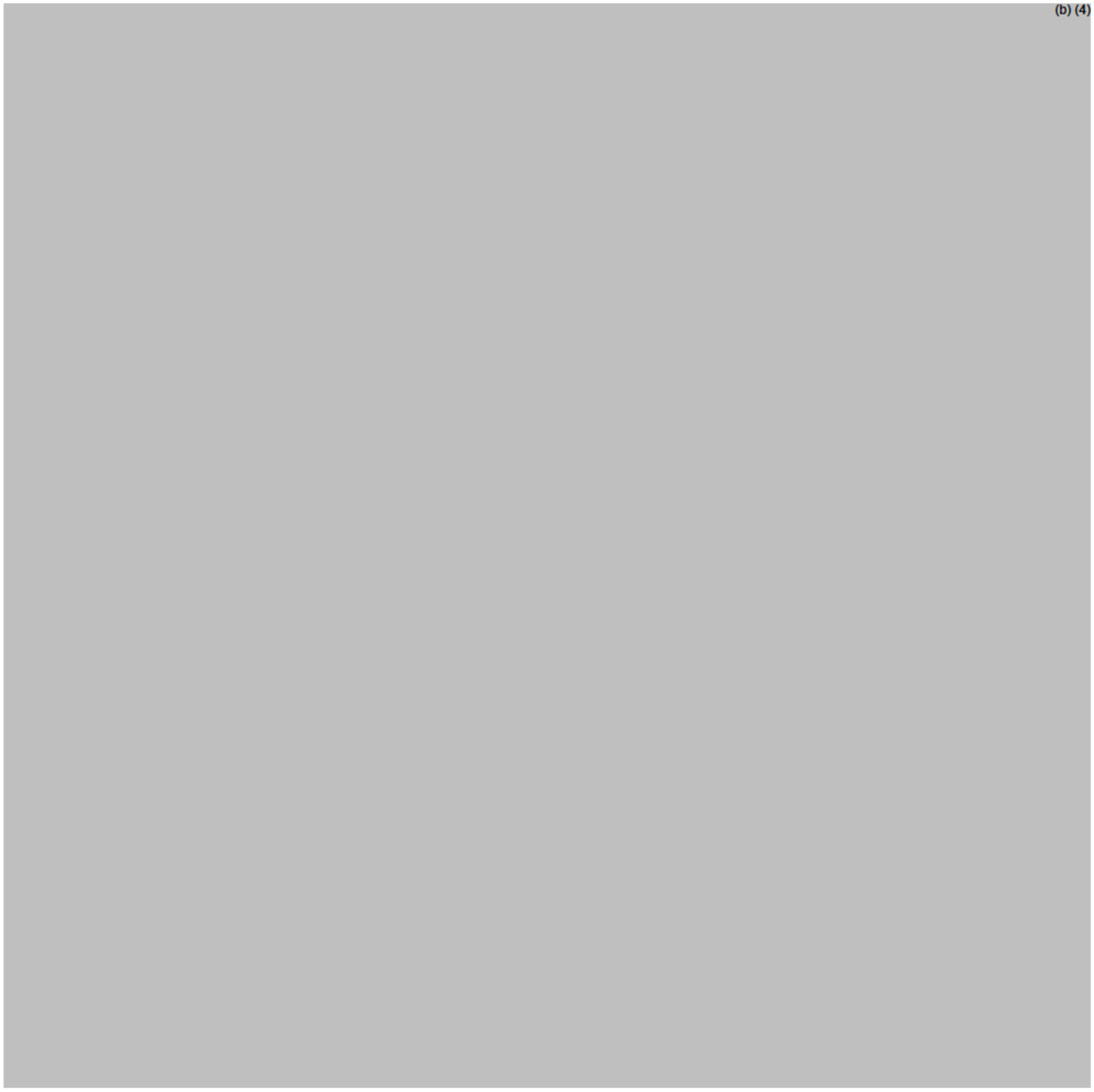


6. The proposed acceptance criteria for the dissolution testing

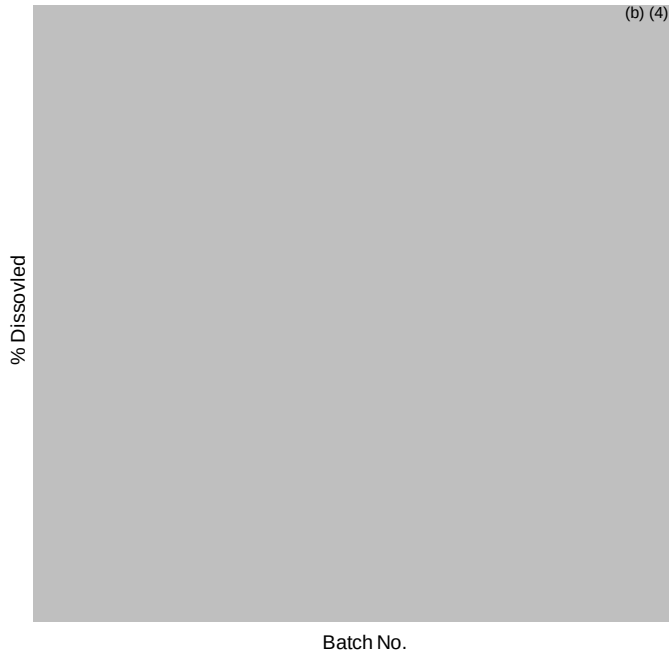
In the original NDA submission dated 2/29/2012, the applicant proposed the following acceptance criteria using the above dissolution method:

1h	Not more than (b) (4)
4h	Between (b) (4) and (b) (4)
8 h	Between (b) (4) and (b) (4)
20 h	Not less than (b) (4)

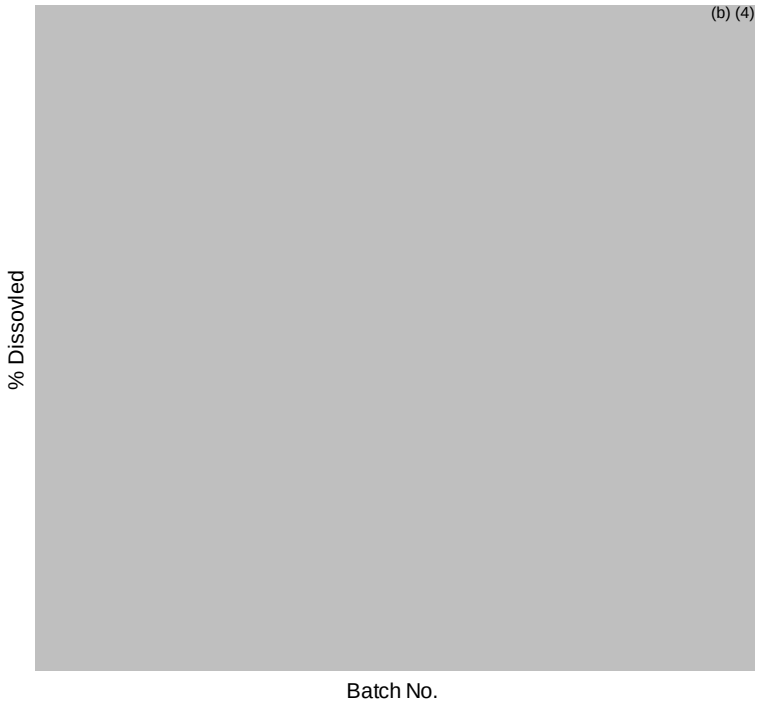
Reviewer's evaluation:

The reviewer's evaluation included the dissolution profile data and the distribution of the dissolution at each time point to determine the appropriate acceptance criteria. The following figure shows the dissolution profiles for the three registration batches.

The following figure shows the distribution of the dissolution at 1 h. The green horizontal line is the proposed acceptance criterion while the red lines are the recommended.



The following figure shows the distribution of the dissolution at 8 h. The green horizontal lines are the proposed acceptance criteria while the red lines are the recommended (note the upper limits are the same).



Based on these evaluations, the following comments were conveyed to the Applicant on 5/11/2012.

> *The proposed dissolution acceptance criteria for the dissolution test need to be revised. Specifically, the following is recommended; 1) to set an acceptance range for the 1 h time point, based on the data provided, we recommend a range of* (b) (4) *2) to tighten the acceptance range to* (b) (4) *for the 8 h time point. We recommend a range of* (b) (4)*, based on the data provided; and 3) to provide additional dissolution data at 10, 12, and 16 hours time points, to explore the possibility of setting* (b) (4) *at a time point earlier than 20 h.*

The Applicant responded on 6/21/2012 and proposed the following revisions.

Time (h)	Existing	Modified
1	Not more than (b) (4)	Between (b) (4) and (b) (4)
4	Between (b) (4) and (b) (4)	Between and
8	Between and	Between and
20	Not less than (b) (4)	Not less than (b) (4)

Reviewer's comments:

The proposed revised acceptance criteria are adequate and acceptable.

7. In vitro alcohol dose dumping study

In the original submission dated 2/29/2012, the in vitro alcohol dose dumping study could not be found. The following information request (IR) was sent to the Applicant on 5/11/2012.

"Please evaluate the alcohol induced dose dumping of your product.

- Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
- The following alcohol concentrations for the in vitro dissolution studies are recommended: 0%, 5%, 10%, 20%, and 40%.
- Dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
- The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.
- The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).
- The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments."

The Applicant provided their responses on 6/21/2012. As recommend, they evaluated the effect of alcohol dose dumping for their ER product, the Applicant conducted dissolution profile analysis on 12 dosage units using the following dissolution parameters. The study was conducted on both the strengths i.e., 50 mg and 100 mg.

Apparatus	Basket (USP Type I)
Agitation	100 RPM
Volume	900 mL
Volume withdrawn	10 mL
Temperature	37.0 ± 0.5°C
Time point	15, 30, 45, 60, 75, 90, 105 and 120 minutes

The following dissolution media were used.

- 0.1N HCl without alcohol (i.e.; 0%) and with alcohol having concentrations of 5%, 10%, 20%, and 40%.
- pH 4.5 Acetate Buffer without alcohol (i.e.; 0%) and with alcohol having concentrations of 5%, 10%, 20%, and 40%.
- pH 6.8 Phosphate Buffer without alcohol (i.e.; 0%) and with alcohol having concentrations of 5%, 10%, 20%, and 40%.

The following analyses were provided with raw data.

- Comparison graphs of *in vitro* dissolution profile are provided for all above recommended dissolution media.
- Calculation for f2 value between the dissolution profiles using 0% alcohol as the reference is provided with the data.

The tables and figures below show the study results using 0.1 N HCl with different alcohol concentrations for 50 mg strength.

(b) (4)

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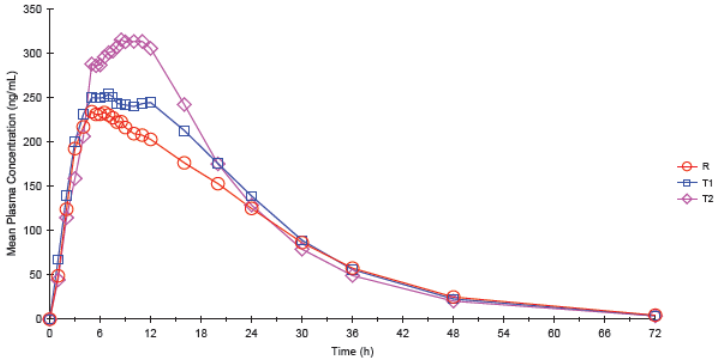
The tables and figure below show the study results using pH 6.8 phosphate buffer with 40% alcohol for 100 mg strength.

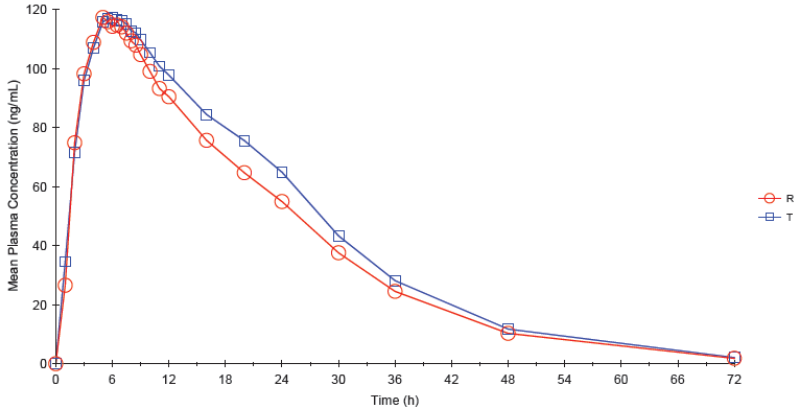
Reviewer's Comments:
The provided in vitro alcohol dose dumping study is acceptable. The results did not show dose dumping potential for both strengths (50 and 100 mg) in all three media (0.1 N HCl, pH 4.5 buffer and pH 6.8 buffer).

8. Extended release claim

This is a 505(b)(2) submission and PRISTIQ® (desvenlafaxine succinate) Extended-Release Tablets was used as the reference listed drug product, which is an approved product with an extended release claim. The following figures show the comparison of the mean plasma concentrations between the test and the reference products for 100 mg strength.



As shown in the figure, the test product under fasting condition (T1) is, on average, slower than the reference product (R), which is approved for the extended release claim. Therefore, the proposed product is expected to show extended release characteristics. Similar situation is observed for 50 mg strength as shown in the following figure.



The Reviewer's Comments: *The extended release characteristics of the proposed products are confirmed.*

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/s/

JOHN Z DUAN
11/25/2012

ANGELICA DORANTES
11/25/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204-150
Product name, generic name of the active, and dosage form and strength	Desvenlafaxine (base) ER Tablets, 50 and 100 mg
Submission Date	February 29, 2012
Applicant	Alembie Pharmaceuticals
Medical Division	DPP
Type of Submission	505(b)(2) NDA
Biopharmaceutics Reviewer	John Duan, Ph.D.
Biopharmaceutics Supervisory Lead	Angelica Dorantes, Ph.D.

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

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

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	X		The following dissolution method is proposed for routine testing: Apparatus: USP 1 (basket) 100 rpm Medium:0.9% NaCl in water, 37ºC, 900 mL
2.	Is the dissolution test part of the DP specifications?	X		Proposed dissolution acceptance criteria: 1 h: Not more than (b) (4) 4 h: Between (b) (4) and (b) (4) 8 h: Between (b) (4) and (b) (4) 20 h: Not less than (b) (4) The proposed criteria are not adequate. The acceptance criterion at 1 h should be a range; the acceptance range for 8 h time point should be tightened to (b) (4) the 20 h time point seems too late.
3.	Does the application contain the dissolution method development report?	X		
4.	Is there a validation package for the analytical method and dissolution methodology?	X		
5.	Does the application include a biowaiver request?		X	Both strengths were tested clinically.
6.	Does the application include an IVIVC model?		X	
7.	Does the application include information/data on in vitro alcohol dose-dumping potential?	X		Although some information is provided, no data could be found in the submission.
8.	Is there any in *vivo* BA or BE information in the submission?	X		

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
9.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		The NDA is filable from the Biopharmaceutics Perspective. However, the comments listed below should be conveyed to the Applicant.
10.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Fileable
12.	Are there any potential review issues identified?	X		1) Alcohol dose dumping study 2) Acceptance criteria of dissolution
13.	**Reviewer Comments** (to be conveyed to the Applicant): 1. We recommend that you evaluate the alcohol induced dose dumping of your MR product. • Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile. • The following alcohol concentrations for the in vitro dissolution studies are recommended: 0%, 5%, 10%, 20%, and 40%. • Dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended. • The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours. • The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference). • The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments. 2. The proposed dissolution acceptance criteria for the dissolution test need to be revised. Specifically, the following is recommended; 1) to set an acceptance range for the 1 h time point, Based on the data provided, we recommend a range of (b) (4). 2) to tighten the acceptance range to (b) (4) for the 8 h time point. We recommend a range of (b) (4), based on the data provided; and 3) to provide additional dissolution data at 10, 12, and 16 hours time points, to explore the possibility of setting (b) (4) at a time point earlier than 20 h.			

{See appended electronic signature page}

John Z. Duan, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

04/23/12
Date

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

{See appended electronic signature page}

Angelica Dorantes, Ph.D. 04/23/12
Acting Biopharmaceutics Supervisory Lead Date
Office of New Drug Quality Assessment

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/s/

JOHN Z DUAN
04/24/2012

ANGELICA DORANTES
04/24/2012