CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204683Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA:	204683
Generic Name:	Desvenlafaxine (base)
Trade Name:	Khedezla®
Strength and Dosage Form:	50 mg and 100 mg Extended Release Tablets
Indication:	Major Depressive Disorder (MDD)
Sponsor:	Osmotica Kft
Submission Type:	Original NDA [505(b)(2)]
Priority Classification:	Standard
Submission Date:	9/13/2012
OCP Division:	DCP1
OND Division:	DPP
Reviewer:	Kofi Kumi, Ph.D.
Team Leader:	Hao Zhu, Ph.D.

Table of Contents

Reference ID: 3317584

Executive Summary

The sponsor submitted Desvenlafaxine base Extended Release (ER) (Khedezla®, Osmotica Kft)) tablets as a 505(b)(2) application using the approved Desvenlafaxine succinate ER (Pristiq®) as the reference product. The development program mainly depended on demonstrating bioequivalence between Khedezla 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:

- Khedezla is bioequivalent to Pristiq at the strengths of 50 mg and 100 mg, under fasting conditions.
- Khedezla is bioequivalent to Pristiq 100 mg under fed conditions.
- Khedezla can be administered with or without food.
- Khedezla exhibits extended release characteristics similar to the approved Pristiq .

1.1 Recommendation

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

1.2 Post Market 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 ± sd terminal half-life, $t_{1/2}$, after administration of Khedezla is about 9.5 ± 1.5 hours. The median (range) time to peak concentration (Tmax) was 6 (3 – 14) hours after administration of 50 mg Khedezla .

Equal doses of Khedezla are bioequivalent to Desvenlafaxine Succinate ER tablets.
Khedezla ER can be administered with or without food.

Reference ID: 3317584

1.4 Summary of Clinical Pharmacology and Biopharmaceutics

Bioequivalence

Khedezla® (Desvenlafaxine base) 100 mg ER tablet was demonstrated to be bioequivalent to Pristiq® (Desvenlafaxine succinate) 100 mg ER Tablet under fasting and fed conditions. Khedezla 50 mg ER tablet was demonstrated to be bioequivalent to Pristiq 50 mg ER tablet under fasting conditions. Tables 1 to 3 contain the statistical results for the comparison of Khedezla (T) to Pristiq (R) 100 mg and 50 mg ER tablets.

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

Parameters	Geometric Least Squares Means (N=35)		(T/R) %	90% CI
	Reference (R)	Test (T)		
Cmax (ng/mL)	215.61	214.38	99.43	92.54 – 106.83
AUC (0-t) (h*ng/mL)	4679.59	4460.28	95.31	86.38 – 105.17
AUC (0-∞) (h*ng/mL)	5035.17	4727.54	93.89	85.02 – 103.68
Tmax* (h)	7.0 (3 – 24)	6.5 (3 – 11)	NA	NA

*Median (range), T = Khedezla, Reference = Pristiq

Table 2: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Desvenlafaxine 100 mg under fed conditions

Parameters	Geometric Mean (N = 33)		(T/R) %	90% CI
	Reference (R)	Test (T)		
Cmax	276.37	282.29	97.9	94.16 – 101.79
AUC (0-t)	5640.98	5763.12	97.88	94.23 – 101.68
AUC (0-∞)	5773.88	5911.24	97.68	93.84 – 101.67
Tmax*	7.71	8.46	NA	NA

*Median (range), T = Khedezla, Reference = Pristiq

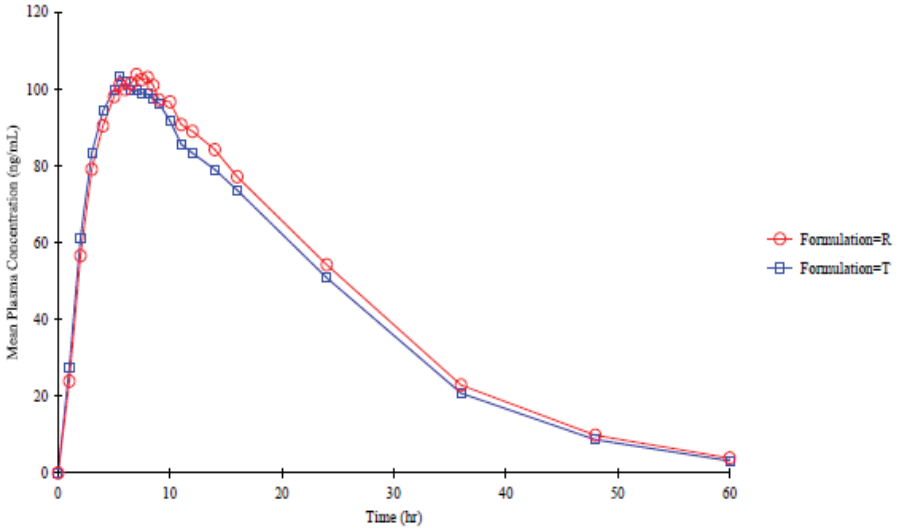
Table 3: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Desvenlafaxine 50 mg under fasting conditions

Parameters	Geometric Mean (N = 33)		(T/R) %	90% CI
	Reference (R)	Test (T)		
Cmax	109.73	108.52	98.90	92.77 – 105.44
AUC (0-t)	2423.03	2280.43	94.11	86.53 – 102.36
AUC (0-∞)	2503.10	2366.66	94.55	87.31 – 102.39
Tmax*	7.00 (4 -24)	6.00 (3 – 14)	NA	NA

*Median (range), T = Khedezla, Reference = Pristiq

The plasma concentration time profiles after administration of Khedezla and Pristiq are similar suggesting that Khedezla exhibits similar extended release characteristics as Pristiq (Figure 1).

Figure 1: Mean plasma concentration-time profile of Desvenlafaxine after administration of 50 mg Pristiq (R) and Khedezla (T) formulations



The Tmax of desvenlafaxine after administration of Khedezla ER and Pristiq ER are comparable under fasting conditions. However, Khedezla median Tmax was later when the study was conducted under fed conditions. The difference in median Tmax when the study was conducted under fed conditions is not expected to be clinically relevant. Therefore, Khedezla can be administered with or without food. After administration of Khedezla 50 mg ER under fasting conditions, there was not a significant difference in half-life for desvenlafaxine when after administration of Khedezla ER (T ½ = 9.78 hours) or Pristiq ER (T ½ = 9.45 hours). Similar results were observed when Khedezla ER or Pristiq ER 100 mg was administered.

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)).

Question Based Review (QBR)

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) application for Desvenlafaxine Extended Release (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 (Osmotica KFT) 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. Figure 2 is the structure of desvenlafaxine.

Figure 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.

Reference ID: 3317584

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 the investigational drug was well tolerated by healthy subjects in the bioequivalence studies. There were no deaths or serious adverse events reported in the study by the sponsor. The sponsor reported that across the three trials, two events were reported by more than a single subject and more in Desvenlafaxine 100 mg ER-treated subjects than Pristiq 100 mg ER-treated subjects: headache (3 subjects in Study OS230-1006, all in the Desvenlafaxine 100 mg ER treatment period) and vomiting (3 subjects in Study 11-VIN-478, 2 subjects in the Desvenlafaxine 100 mg ER treatment period and 1 subject in the Pristiq 100 mg ER treatment period). Headache was not reported in Study 11-VIN-478 or Study 11-VIN-479. Vomiting was reported by 1 subject in each treatment period in Study OS230-1006, and by 3 subjects in treatment period in Study 11-VIN-479. 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.

A Relative Bioavailability Study of Desvenlafaxine 100 mg ER tablets versus Pristiq 100 mg under Fed Conditions (Study OS230-1006).

A Randomized, Open Label, Two Treatment, Two Period, Two Sequence, Single Dose, Crossover, Oral Comparative Bioavailability Study Of Desvenlafaxine Extended Release Tablets 50mg of Osmotica Kft and PRISTIQ® Extended Release Tablets 50mg of Wyeth Pharmaceuticals Inc., USA in Healthy, Adult, Human Subjects, Under Fasting Condition (Study 11-VIN-478); and

A Randomized, Open Label, Two Treatment, Two Period, Two Sequence, Single Dose, Crossover, Oral Comparative Bioavailability Study of Desvenlafaxine Extended Release Tablets 100mg of Osmotica Kft and PRISTIQ® Extended Release Tablets 100mg of Wyeth Pharmaceuticals Inc., USA in Healthy, Adult, Human Subjects, under Fasting Condition (Study 11-VIN-479)

2.2.2 Is Desvenlafaxine (Khedzla®, Osmotica) 100 mg ER bioequivalent to the reference listed drug, Pristiq (desvenlafaxine succinate) 100 mg ER under fasting conditions?

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

The sponsor conducted a single dose, randomized, open-label, 2-period bioequivalence study in healthy subjects to demonstrate that Desvenlafaxine base (Khedezla, Osmotica) was bioequivalent to Desvenlafaxine succinate (Pristiq, Wyeth) under fasting conditions. The mean plasma concentration-time profiles after administration of 100 mg Khedezla or 100 mg Pristiq under fasting conditions are provided in Figure 3.

Figure 3: Mean Plasma Concentration Time profile for Desvenlafaxine

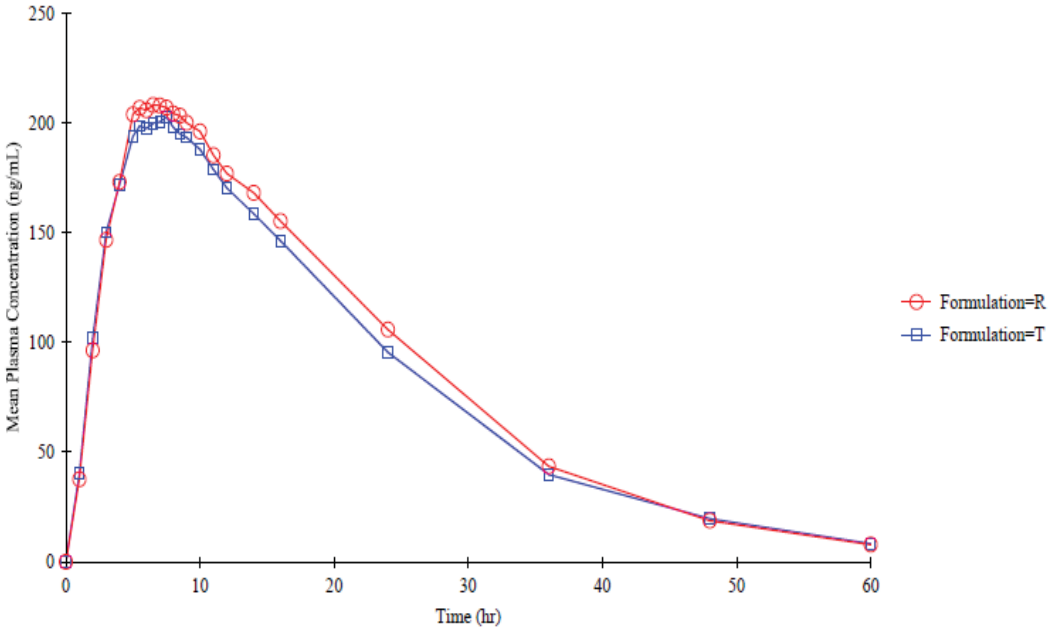


Table 4 contains the statistical analysis for Desvenlafaxine. R refers to Pristiq and T to Khedezla.

Table 4: Geometric Least Squares Means, Ratios and 90% Confidence Interval for Desvenlafaxine 100 mg under fasting conditions

Parameters	Geometric Least Squares Means (N=35)		(T/R) %	90% CI
	Reference (R)	Test (T)		
Cmax (ng/mL)	215.61	214.38	99.43	92.54 – 106.83
AUC (0-t) (h*ng/mL)	4679.59	4460.28	95.31	86.38 – 105.17
AUC (0-∞) (h*ng/mL)	5035.17	4727.54	93.89	85.02 – 103.68
Tmax* (h)	7.0 (3 – 24)	6.5 (3 – 11)	NA	NA

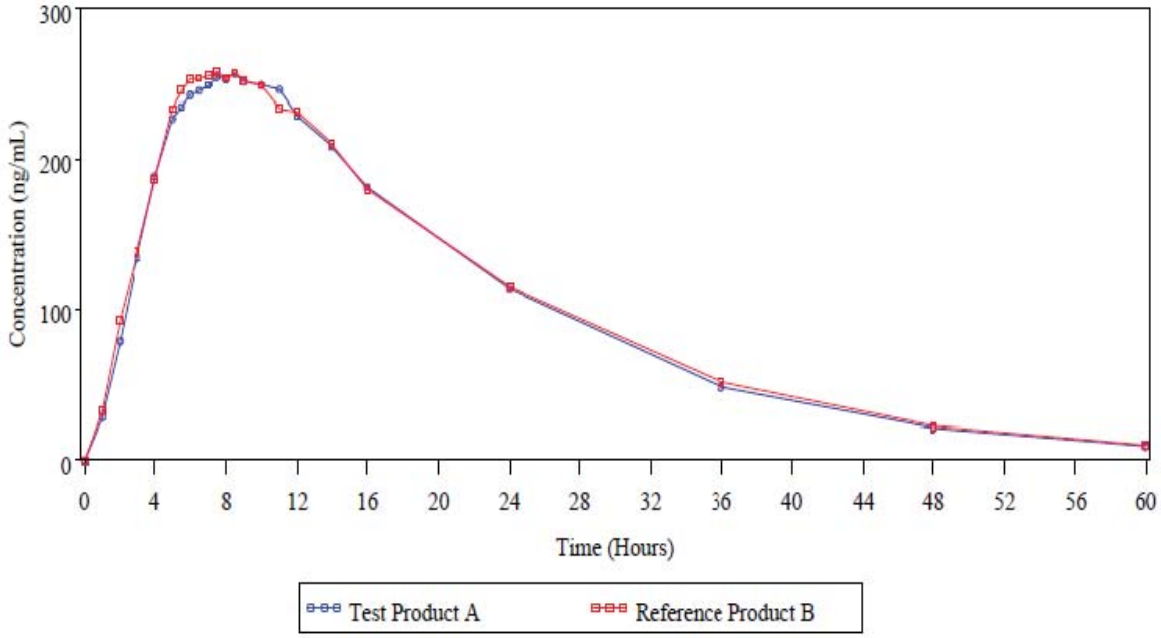
R= Pristiq, T= Desvenlafaxine base (Osmotica, Khedezla), *Median (range). Geometric Means are based on LSM of ln-transformed values

The 90% confidence intervals (CIs) of the ratios of Cmax, AUC (0-t), and AUC(0-∞) between test and reference are within the regulatory criteria (80% to 125%) for bioequivalence; therefore, Khedezla is bioequivalent to Pristiq. The mean half-life for Desvenlafaxine after administration of Khedezla and Pristiq were 10.6 and 10.4 hours, respectively.

2.2.3 Is the exposure to Desvenlafaxine significantly different after administration of Desvenlafaxine (ER (Khedezla) 100 mg and Pristiq 100 mg when administered under fed conditions?

The Sponsor assessed the bioequivalence of Desvenlafaxine after administration of Khedezla and Pristiq under fed conditions. The study was a single dose, randomized, open label, cross over, 2-period study in healthy volunteers. Figure 4 is the mean plasma concentration time curve for Desvenlafaxine after administration of 100 mg Pristiq or 100 mg Khedezla.

Figure 4: Mean Plasma Concentration-Time profile for Desvenlafaxine



Test Product A = Khedezla, Reference Product B = Pristiq

Table 5 is the statistical evaluation for Desvenlafaxine after administration of Khedezla or Pristiq under fed conditions.

Table 5: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Desvenlafaxine 100 mg under fed conditions

Parameters	Geometric Mean (N = 33)		(T/R) %	90% CI
	Reference (R)	Test (T)		
Cmax	276.37	282.29	97.9	94.16 – 101.79
AUC (0-t)	5640.98	5763.12	97.88	94.23 – 101.68
AUC (0-∞)	5773.88	5911.24	97.68	93.84 – 101.67
Tmax*	7.71	8.46	NA	P = 0.09

Test = Khedezla, Reference = Pristiq. *Median

The 90% CIs of the ratios of the test to reference parameters fall within the regulatory criteria (80% to 125%); therefore, Khedezla and Pristiq are bioequivalent under fed conditions. Median Tmax for Pristiq and Khedezla were not significantly different. Comparing the Tmax results from the study under fasting conditions (11-VIN-479), food appears to have increased Tmax by about 1 hour. This increase is not expected to be clinically relevant.

2.2.4 Is Khedezla® (desvenlafaxine base) 50 mg ER bioequivalent to the reference listed drug, Pristiq® (desvenlafaxine succinate) 50 mg ER under fasting conditions?

Khedezla (desvenlafaxine base) Extended Release Tablets 50mg when compared with Pristiq® Extended Release Tablets 50mg meets the regulatory criteria for bioequivalence. Therefore, Khedezla is bioequivalent to Pristiq.

The sponsor conducted a randomized, open label, two treatment, two period, two sequence, single dose, crossover study to evaluate the bioequivalence of Khedezla® (Desvenlafaxine base) Extended Release Tablets 50mg and Pristiq® Extended Release Tablets 50mg in healthy, adult, human subjects, under fasting condition. Figure 5 provides the plasma concentration time profile after administration of Khedezla or Pristiq 50 mg Extended Release tablets.

Figure 5: Mean plasma concentration-time profile of Desvenlafaxine after administration of Pristiq (R) and Khedezla (T) formulations

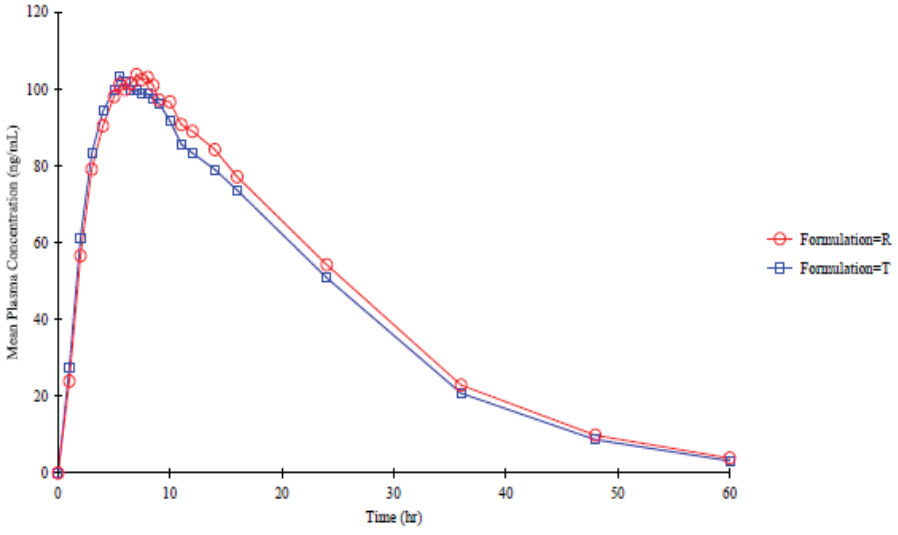


Table 6 contains the results of the statistical evaluation for bioequivalence after administration of Pristiq or Khedezla 50 mg ER tablets after fasting conditions.

Table 6: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Desvenlafaxine 50 mg under fasting conditions

Parameters	Geometric Mean (N = 33)		(T/R) %	90% CI
	Reference (R)	Test (T)		
Cmax	109.73	108.52	98.90	92.77 – 105.44
AUC (0-t)	2423.03	2280.43	94.11	86.53 – 102.36
AUC (0-∞)	2503.10	2366.66	94.55	87.31 – 102.39
Tmax*	7.00 (4 -24)	6.00 (3 – 14)	NA	NA

*Median (range)

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

After administration of Khedezla (Desvenlafaxine) 50 mg ER by Osmotica Pharmaceuticals, the mean elimination half-life (T ½) was 9.5 ± 1.5 hours which is similar to that observed after administration of Pristiq (9.8 ± 1.4 hours). The median (range) time to peak concentration (Tmax) was 6.0 (3 – 14) 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).

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

Table 7 contains the qualitative and quantitative composition of Khedezla (Desvenlafaxine) ER tablets.

Table 7: Components and Composition of Desvenlafaxine ER Tablets 50 and 100 mg

Materials	Quality	Function	mg per tablet	% w/w	mg per /tablet	% w/w
Desvenlafaxine Base Drug Substance	In-house Spec.	API	50.0	(b) (4)	100.0	(b) (4)
Hypromellose (b) (4) (b) (4)	USP		(b) (4)		(b) (4)	
Citric Acid, Monohydrate, (b) (4)	USP					
Microcrystalline Cellulose and Colloidal Silicon Dioxide (b) (4)	USP					
Talc (b) (4)	USP					
Magnesium Stearate (b) (4) (b) (4) (b) (4)	NF					
(b) (4) Film Coating (b) (4)	Proprietary					
Total-Film Coated Tablets			517.5 mg	100%	517.5 mg	100%

(b) (4)

Analytical Methods

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.

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 calibration range of the method is 2 to 1000 ng/mL using a 50.0 µL aliquot of plasma. The method was sensitive, selective, accurate, and reproducible. O-desmethylvenlafaxine is stable during storage, processing and analysis in human plasma samples. The analytical method was adequately validated and acceptable. The following is a tabular summary of the validation of the bioanalytical method.

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.4, analyt-validation.pdf
Analyte	O-Desmethylvenlafaxine
Internal standard (IS)	O-Desmethyl Venlafaxine-d10
Method description	Protein precipitation extraction with LC-MS/MS method
Limit of quantitation (ng/mL)	2.000 ng/mL
Average recovery of drug (%)	73.17%
Average recovery of IS (%)	111.7%
Standard curve concentrations (ng/mL)	2.000, 4.000, 10.00, 20.00, 40.00, 100.0, 400.0, 800.0, 1000 ng/mL
QC concentrations (ng/mL)	6.000, 60.00 and 750.0 ng/mL
QC Intraday precision range (%)	1.0 to 5.7%
QC Intraday accuracy range (%)	-14.6 to -8.1%
QC Interday precision range (%)	2.4 to 4.3%
QC Interday accuracy range (%)	-14.0 to -9.1%
Bench-top stability (hrs)	24 hours in human plasma @ room temperature
Stock stability (days/hours)	6 hours @ room temperature for drug and internal standard Drug: Provided by manufacturer @ 5°C Internal standard: Established as the non-labeled molecule O-desmethylvenlafaxine @ 5°C
Processed stability (hrs)	97 hours @ room temperature
Freeze-thaw stability (cycles)	5 freeze-thaw cycles
Long-term storage stability (days)	7 days @ -20°C
Dilution integrity	5000 ng/mL diluted 10-fold
Selectivity	No interfering peaks noted in blank plasma samples

4. Appendix

4.1 Individual Studies

Biopharmaceutics

Report #: OS230-1006 (C10-2062, S11-0011)	**Study Period**: October 27, 2011 to November 6, 2011	EDR Link: \\Cdsesub1\evsprod\nda204683\0000\m5\53-clin-stud-rep

Title	A Relative Bioavailability Study of Desvenlafaxine 100 mg ER Tablets Versus Pristiq 100 mg ER Tablets Under Fed Conditions
Objective	To assess the relative bioavailability of Desvenlafaxine 100 mg ER Tablets compared to that of Pristiq 100 mg ER Tablets following a single oral dose (1 x 100 ER mg tablet) in healthy adult subjects when administered under fed conditions.

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	36 hours Inpatient stay ☑Y ☐ N:

Treatments: (Active: Desvenlafaxine)
Meal: FDA Standardized High Fat Meal (2 eggs cooked in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, 8 fluid ounces of whole milk)

	Test	**Reference**
Dosage Form	ER Tablets	Pristiq ER
Dosage Strength	100 mg	100 mg
Batch #.	B110515	E99244
Administration	Oral	Oral
Manufacture	Osmotica	Wyeth

Sampling Times (PK, plasma)

- Test : 0 (predose), 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 24, 36, 48, and

Reference ID: 3317584

60 hours post dose

- Reference: 0 (predose), 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 24 36, 48, and 60 hours post dose
-

Analytical Method: The performance of the analytical method is acceptable. Yes ☑ No ☐
LC/MS/MS. Calibration range 2 to 1000 ng/mL

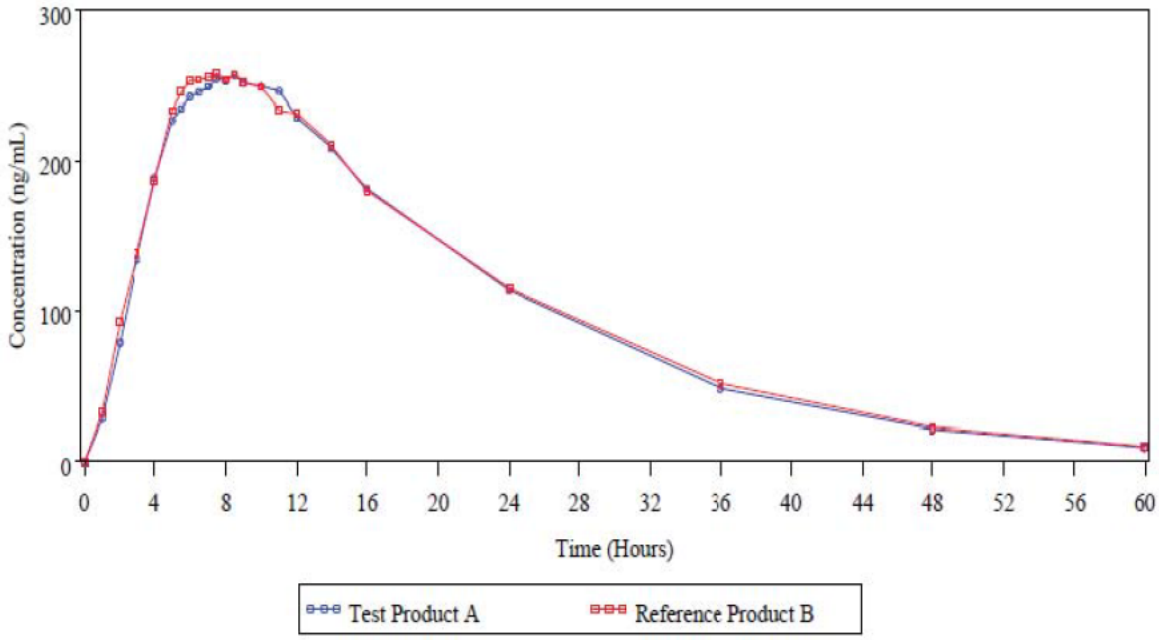
Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed. %CV < 15%, %Bias > -14%.

Study Population :

Randomized/Completed/ Discontinued Due to AE	36/33/1
Age [Mean ± SD (range)] years	35.3 ± 9.9 (20 – 53)
Male/Female	21/15
Race (Caucasian/Black/Asian/other)	17/14/1/1

Results

Mean plasma concentration for Desvenlafaxine



Parameters	Geometric Mean (N = 33)		(T/R) %	90% CI
	Reference (R)	Test (T)		
Cmax	276.37	282.29	97.9	94.16 – 101.79
AUC (0-t)	5640.98	5763.12	97.88	94.23 – 101.68
AUC (0-∞)	5773.88	5911.24	97.68	93.84 – 101.67
Tmax	7.71	8.46	NA	P = 0.09

Site Inspected

Reference ID: 3317584

Requested: Yes☑ No ☐	**Performed:** Yes☐ No ☐ N/A ☐
Safety	
▪ Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA The sponsor reported that overall, the most common AEs reported were nausea, headache, and vomiting. Nausea was reported on at least one occasion in 4 (4/36) subjects (11.11%). Headache was reported on one occasion in 3 (3/36) subjects (8.33%). Vomiting was reported on one occasion in 2 (2/36) subjects (5.56%). The frequently reported adverse events were nausea, vomiting and headache. The sponsor reported that overall Desvenlafaxine 100 mg ER tablets (Osmotica) were well tolerated.	
Conclusion	
The results of this study indicate that bioequivalence criteria were met when Osmotica Kft.'s Desvenlafaxine 100 mg ER Tablets and Pristiq 100 mg ER Tablets were administered under fed conditions.	
Comments	
The reviewer agrees with the sponsor's conclusions. Tmax was not significantly affected when administered under fed conditions.	

Biopharmaceutics

Report #: OS230-1007 (11-VIN-478)	**Study Period**: June 24, 2012 to July 4, 2012	EDR Link: \\Cdsesub1\evsprod\nda204683\0000\m5\53-clin-stud-rep
Title	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, oral comparative bioavailability study of Desvenlafaxine Extended Release Tablets 50mg of Osmotica Kft and Pristiq® Extended Release Tablets 50mg of Wyeth Pharmaceuticals Inc., USA in healthy, adult, human subjects, under fasting condition	
Object- ive	To compare and evaluate the single-dose oral comparative bioavailability of Desvenlafaxine Extended Release Tablets 50mg of Osmotica Kft and Pristiq® Extended Release Tablets 50mg of Wyeth Pharmaceuticals Inc., USA in healthy, adult, human subjects, under fasting condition as well as to monitor for adverse events and ensure the safety of subjects.	
Study Design		
☑Bioequivalence	☐ Bioavailability	
Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers		
Screening: ≤ 28 days	**Washout:** ≥ 7days, outpatient	
Period 1/2	2 days, Inpatient stay ☑Y ☐ N:	
Treatments: (Active Ingredient: Desvenlafaxine)		

	Test	Reference
Dosage Form	ER	Pristiq® ER
Dosage Strength	50 mg	50 mg
Batch #.	B120137	F51192
Administration	Oral	Oral

Sampling Times (PK, plasma)

- Test : 0 (pre-dose), 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 24, 36, 48, 60 hours post dose
- Reference: 0 (pre-dose), 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 24, 36, 48, 60 hours post dose

Analytical Method: The performance of the analytical method is acceptable. Yes ☑ No ☐
Method: HPLC-ESI-MS/MS. Calibration Curve (CC) range: 3 to 750 ng/mL
QC samples: Precision (CV%): ≤ 7.26%, Accuracy (%Bias) = -1.56 to 1.17
CC samples: Precision (CV%) ≤ 6.56 , Accuracy (%Bias) = -2.50 to 2.40

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	42/38//3
Age [Mean ± SD (range)] years	28.9 ± 5.7 (19 - 42)
Male/Female	28/14
Race (Caucasian/Black/Asian/other)	N/A

Results

Mean Pharmacokinetic Parameters estimated for reference (R) and Test (T) products

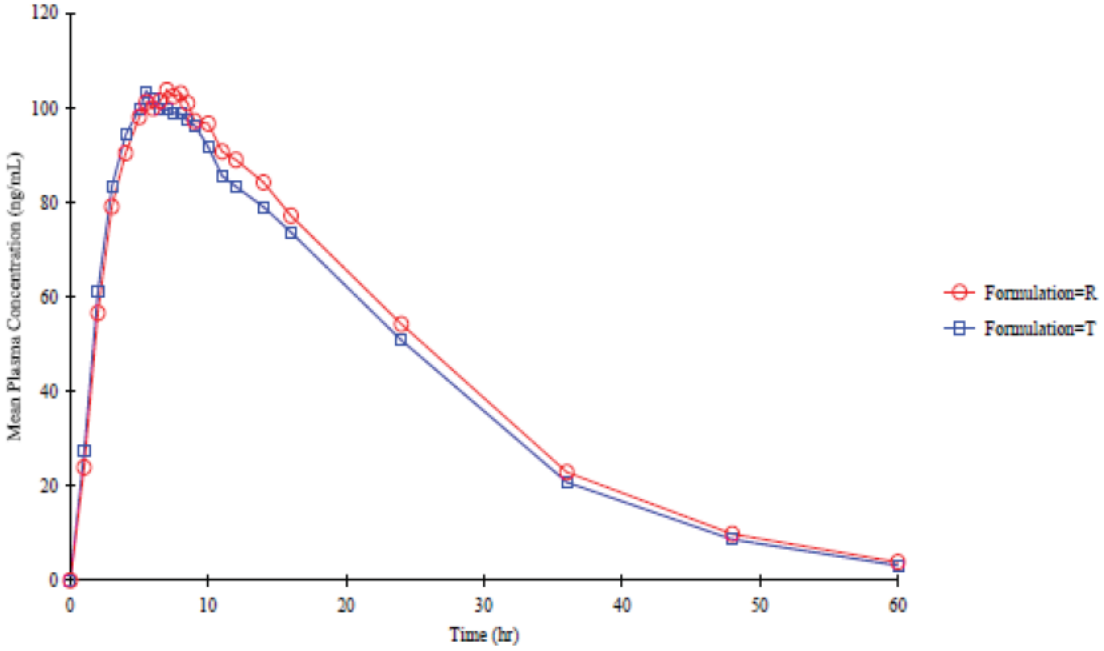
Parameters (Units)	Mean ± SD (N = 36)	
	Reference product (R)	Test product (T)
$^{+}T_{max}$ (h)	7.000 (4.00 - 24.00)	6.000 (3.00 - 14.00)
C_{max} (ng/mL)	114.710 ± 33.5828	112.185 ± 30.2233
AUC_{0-t} (hr*ng/mL)	2581.895 ± 871.4037	2460.345 ± 936.6981
AUC_{0-inf} (hr*ng/mL)	2662.738 ± 897.5032	2542.991 ± 958.7692
K_{el} (1/hr)	0.0723 ± 0.01043	0.0750 ± 0.01155
$t_{½}$ (hr)	9.778 ± 1.4180	9.453 ± 1.4670

$^{+}$ For T_{max} median (min – max)

Reference ID: 3317584

Parameters (Units)	Ln-transformed Geometric Least Squares Means and it's ratio (N = 36)			Intra subject %CV	90% Confidence Interval	Power
	Reference Product (R)	Test Product (T)	(T/R)%			
C_{max} (ng/mL)	109.727	108.521	98.90%	16.61%	92.77% - 105.44%	99.99%
AUC_{0-t} (hr*ng/mL)	2423.030	2280.434	94.11%	21.91%	86.53% - 102.36%	99.59%
AUC_{0-inf} (hr*ng/mL)	2503.103	2366.659	94.55%	20.76%	87.31% - 102.39%	99.78%

Mean plasma concentration-time profile of Desvenlafaxine after administration of Reference (R) and Test (T) formulations



Site Inspected

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

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- The sponsor reported that three subjects (subject numbers 03, 04 and 22) reported adverse events after administration of test product. Subject 3 and 4 reported vomiting. In subject 22, there was increased bilirubin. Subject number 37 reported vomiting events after administration of reference product. No significant or serious adverse event occurred during the conduct of the study.

Conclusion

The Test Product (T) (Desvenlafaxine Extended Release Tablets 50mg of Osmotica Kft) when compared with the Reference Product (R) (Pristiq® Extended Release Tablets 50mg of Wyeth Pharmaceuticals Inc., USA) meets the bioequivalence criteria in terms of rate and extent of absorption after administration of single dose as set in the protocol.
Comments
Reviewer agrees with the sponsor's conclusions. The two products at the strength of 50 mg are bioequivalent.

Biopharmaceutics

Report #: OS230-1009 (11-VIN-479)	**Study Period**: June 28, 2012 to July 8, 2012	EDR Link: \\Cdsesub1\evsprod\nda204683\0000\m5\53-clin-stud-rep

Title	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, oral comparative bioavailability study of Desvenlafaxine Extended Release Tablets 100mg of Osmotica Kft and Pristiq® Extended Release Tablets 100mg of Wyeth Pharmaceuticals Inc., USA in healthy, adult, human subjects, under fasting condition.
Objective	To compare and evaluate the single-dose oral comparative bioavailability of Desvenlafaxine Extended Release Tablets 100mg of Osmotica Kft and Pristiq® Extended Release Tablets 100mg of Wyeth Pharmaceuticals Inc., USA in healthy, adult, human subjects, under fasting condition as well as to monitor for Adverse Events and ensure the safety of subjects

Study Design	
☑Bioequivalence	☐ Bioavailability
Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers	
Screening: ≤ 28 days	**Washout:** ≥ 7days, outpatient
Period 1/2	36 hours, Inpatient stay ☑Y ☐ N:

Treatments: (Active Ingredient: Desvenlafaxine)

	Test	**Reference**
Dosage Form	ER	Pristiq® ER
Dosage Strength	100 mg	100 mg
Batch #.	B120138	E99244
Administration	Oral	Oral

Sampling Times (PK, plasma)

- Test : 0 (pre-dose), 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 24, 36, 48, 60 hours post dose
- Reference: 0 (pre-dose), 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 24, 36,

Reference ID: 3317584

48, 60 hours post dose

Analytical Method: The performance of the analytical method is acceptable. Yes ☑ No ☐
Method: HPLC-ESI-MS/MS. Calibration curve (CC) range 3 to 750 ng/mL
QC samples: Precision (CV%): ≤ 5.03%, Accuracy (%Bias) = -4 to -1.33

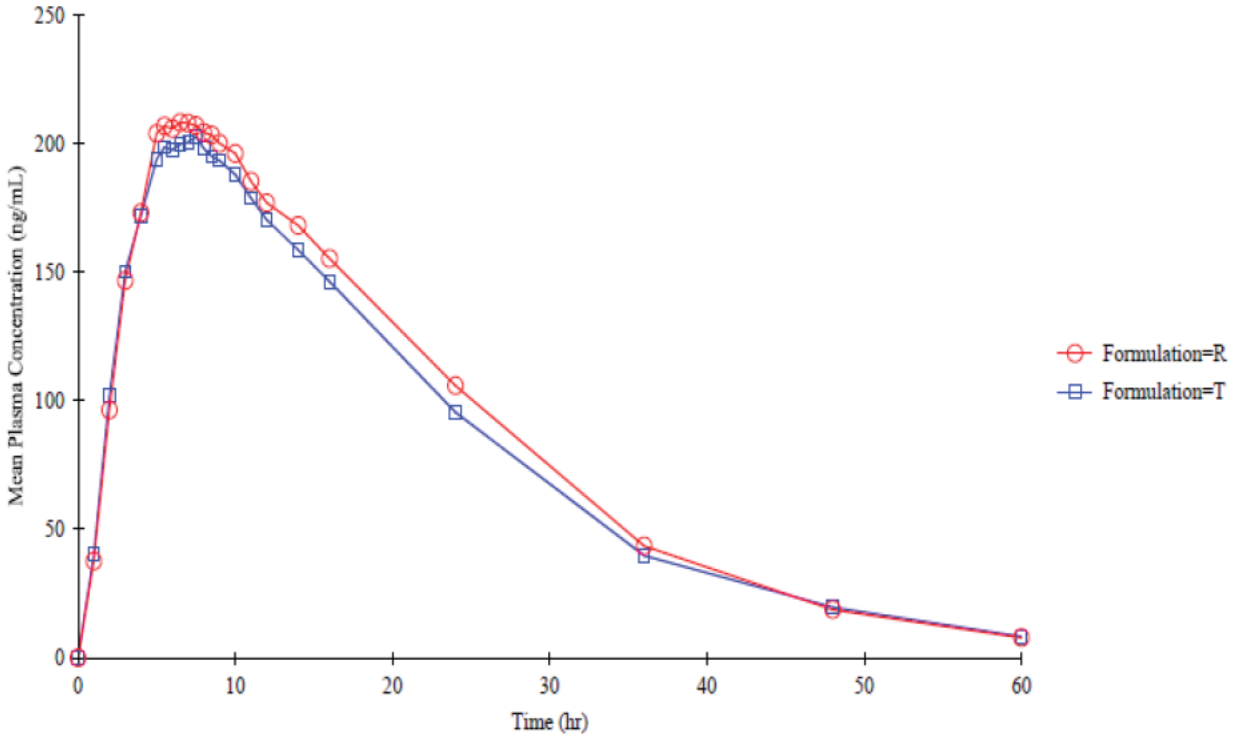
Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	42/35/5
Age [Mean ± SD (range)] years	31.26 ± 6.32 (18 to 41)
Male/Female	28/14
Race (Caucasian/Black/Asian/other)	NA

Results

Mean plasma concentration time profile for desvenlafaxine



Mean Pharmacokinetic Parameters for Reference (R) and Test (T)

Reference ID: 3317584

Parameters (Units)	Mean ± SD (N = 35)	
	Reference product (R)	Test product (T)
$^{+}T_{max}$ (h)	7.000 (3.00 - 24.00)	6.500 (3.00 - 11.00)
C_{max} (ng/mL)	226.969 ± 70.7776	220.582 ± 57.7648
AUC_{0-t} (hr*ng/mL)	4908.080 ± 1546.0981	4807.837 ± 1809.6713
AUC_{0-inf} (hr*ng/mL)	5390.441 ± 1968.9921	5100.523 ± 1986.8400
K_{el} (1/hr)	0.0709 ± 0.01557	0.0701 ± 0.01484
$t_{½}$ (hr)	10.436 ± 3.3184	10.583 ± 3.8200

$^{+}$ For T_{max} median (min – max)

Parameters	Ln-transformed Geometric Least Squares Means (N=35)		(T/R) %	90% CI
	Reference (R)	Test (T)		
Cmax	215.61	214.38	99.43	92.54 – 106.83
AUC (0-t)	4679.59	4460.28	95.31	86.38 – 105.17
AUC (0-∞)	5035.17	4727.54	93.89	85.02 – 103.68

Site Inspected

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

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- The sponsor reported that no significant or serious adverse event occurred during the conduct of the study. Vomiting was the most frequent adverse event reported.

The most common adverse event reported was vomiting.

Conclusion

The study results indicated that the bioequivalence criteria were met. The 90% confidence interval for the geometric mean ratio for Cmax, AUC(0-t) and AUC(0-∞) were contained with the regulatory acceptance range of 80% to 125%. Mean Tmax for the two formulations were not significantly different

Comments

The reviewer agrees that the two products at the strength of 100 mg are bioequivalent.

4.2 OSI Report

4 Pages Have Been Withheld As A Duplicate Copy Of The "OSI Report" dated May 7, 2013 Which Is Located In The Other Review Section Of This NDA Approval Package.

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

/s/

KOFI A KUMI
05/31/2013

HAO ZHU
05/31/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204683	**Biopharmaceutics Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	September 13, 2012		
Division:	Division of Psychiatry Products	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Applicant:	Osmotica Kereskedelmies Szolgaltato Kft	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	Khedezla (desvenlafaxine) Extended Release Tablets	**Date Assigned:**	September 24, 2012
Generic Name:	Desvenlafaxine	**Date of Review:**	May 9, 2013
Indication:	Treatment of major depressive disorder	**Type of Submission:** 505(b)(2) Original New Drug Application	
Dosage form/ strengths	Extended Release Tablet/ 50 mg/tablet and 100 mg/tablet		
Route of Administration	Oral		

SUMMARY

Submission: This 505(b)(2) New Drug Application is for an extended release (ER) film coated desvenlafaxine tablet indicated for the treatment of major depressive disorder. Desvenlafaxine ER tablets contain 50 mg or 100 mg desvenlafaxine free base. The proposed drug product is a (b) (4) drug product, formulated to exhibit extended release properties. This application is an electronic NDA, filed as a 505(b)(2) application, with Pristiq® (NDA 21992) as the reference product.

Review: The Biopharmaceutics review for this NDA is being focused on the evaluation and acceptability of 1) the proposed dissolution methodology, 2) the dissolution acceptance criteria, 3) the in vitro alcohol dose dumping study, 4) the extended release claim, and 5) (b) (4)

RECOMMENDATION:

ONDQA-Biopharmaceutics has evaluated the information provided in NDA 204683 and concludes the following:

- The dissolution method and acceptance criteria as summarized below are acceptable.

Dissolution method:

USP Apparatus I (basket)

Reference ID: 3306579

Temperature: 37 °C
Rotation speed: 75 rpm
Medium: 900 mL 0.9% NaCl in water

Dissolution acceptance criteria:

50 mg tablet: Hour 2: (b) (4)%
Hour 8: (b) (4)%
Hour 12: NLT (b) (4)%

100 mg tablet: Hour 2: (b) (4)%
Hour 8: (b) (4)%
Hour 12: NLT (b) (4)%

- In vitro alcohol dose dumping study:
  Dose dumping in the presence of alcohol does not occur in vitro.

- Extended release claim:
  The extended release claim for the proposed drug product is acceptable.

- (b) (4)

From the Biopharmaceutics perspective, NDA 204683 for Khedezla (desvenlafaxine) Extended Release Tablets (50 and 100 mg/tablet) is recommended for **APPROVAL**.

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES

SUBMISSION:

This 505(b)(2) New Drug Application is for an extended release film coated desvenlafaxine tablet indicated for the treatment of major depressive disorder. Desvenlafaxine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). Desvenlafaxine ER Tablets 50 mg and 100 mg are (b) (4) manufactured from desvenlafaxine free base. (b) (4) The drug product was designed to be bioequivalent to Pristiq®. This application is an electronic NDA, filed as a 505(b)(2) application, with Pristiq® (NDA 21992) as the reference product, however, instead of using the desvenlafaxine succinate used in the reference product as the drug substance this Applicant (Osmotica) chose to use the desvenlafaxine free base (b) (4) There are (b) (4)

BIOPHARMACEUTICS INFORMATION:

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of
1) the proposed dissolution methodology,
2) the dissolution acceptance criteria,
3) the in vitro alcohol dose dumping study,
4) the extended release claim, and
5) (b) (4)

Composition of the proposed 50 mg and 100 mg tablets:

Materials	Quality	Function	mg per tablet	% w/w	mg per /tablet	% w/w
Desvenlafaxine Base Drug Substance	In-house Spec.	API	50.0	(b) (4)	100.0	(b) (4)
Hypromellose (b) (4) (b) (4)	USP	(b) (4)	(b) (4)			(b) (4)
Citric Acid, Monohydrate, (b) (4)	USP					
Microcrystalline Cellulose and Colloidal Silicon Dioxide (b) (4)	USP					
Talc (b) (4)	USP					
Magnesium Stearate (b) (4)	NF					
(b) (4) Film Coating (b) (4)	Proprietary					
Total-Film Coated Tablets			517.5 mg		517.5 mg	(b) (4)
						(b) (4)

DISSOLUTION METHOD:

The proposed dissolution method is:

USP Apparatus I (basket)
Temperature: 37 °C
Rotation speed: (b) (4) rpm
Medium: 900 mL 0.9% NaCl in water
Sampling time points: 1, 2, 4, 8, 12, 16, 20, and 24 hours

The Applicant has noted that the dissolution parameters of the proposed method are (b) (4) The dissolution method development report describes the selection of the dissolution test conditions as follows:

Selection of apparatus:

(b) (4)

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Reference ID: 3306579

(b) (4)

Reviewer's Assessment of the proposed dissolution method:

The Applicant has justified the selected dissolution apparatus and dissolution medium. The discriminating power of the dissolution method has been demonstrated. The rotation speed should (b) (4) *75 rpm,* (b) (4)

Information request dated 2/28/13:

Revise your dissolution method to include a rotation speed of 75 rpm instead of (b) (4) *rpm.*

Applicant's response dated 3/21/13:

As indicated in the response to Drug Product Question 6 below, Osmotica would like to collect additional data to verify that the change in the dissolution basket rotation speed to 75 RPMs is appropriate for controlling the quality of Desvenlafaxine ER Tablets 50 mg and 100 mg and will provide the data and a specification proposal by April 8, 2013.

Applicant's response dated 4/5/13:

The data obtained from dissolution studies on 3 lots of Desvenlafaxine ER Tablets, 50 mg are provided in Table 1 through Table 6 and 3 lots of Desvenlafaxine ER Tablets, 100 mg are provided in Table 7 through Table 12. (b) (4) *Based on the results of this study, Osmotica has adopted the FDA request to revise the rotation speed of the method to 75 RPM. The method has been updated and has been submitted to the NDA.*

Reviewer's Overall Assessment of the dissolution method and the dissolution method validation: Acceptable

The Applicant has revised the rotation speed to 75 rpm as requested. The revised dissolution method is found acceptable.

DISSOLUTION ACCEPTANCE CRITERIA:

The proposed dissolution acceptance criteria are:

Level 1 (N=6)

No individual value lies outside the stated % release ranges of:

Hour 2: (b) (4)
Hour 8:
Hour (b) (4) NLT (b) (4)

Level 2 (N=12)

Average value for all units are within the % released ranges:

Hour 2: (b) (4)
Hour 8:
Hour (b) (4) NLT (b) (4)% and

Each unit must be within:

Hour 2: (b) (4)
Hour 8:
Hour (b) (4) No individual unit is LT (b) (4)%

Level 3 (N=24)
Average value for all units are within the % released ranges:
Hour 2: (b) (4)
Hour 8:
Hour (b) (4) NLT (b) (4)% and
NMT 2 individual units of 24 units are outside the % release of:
Hour 2: (b) (4)
Hour 8:
Hour (b) (4) NLT (b) (4)
None of the individual units of 24 units are outside the % release of:
Hour 2: (b) (4)
Hour 8:
Hour (b) (4) NLT (b) (4)%

The Applicant states that the proposed acceptance criteria are based on results from clinical batches:

Table 2 **Dissolution Data at Release and on Stability for Bio Lots, 30 Count Bottles**

(b) (4)

Reviewer's Assessment of the proposed dissolution acceptance criterion:
The proposed acceptance criteria (b) (4) *and not supported by the provided data, and therefore are not acceptable. Dissolution acceptance criteria with ranges of mean ± 10% are standard for extended release solid oral dosage forms. The following information request was sent to the Applicant on 2/28/13:*

Information request dated 2/28/13:
Revise your dissolution acceptance criteria to a range of ± 10% of target for the 2 hour and 8 hour time points.

Applicant's response dated 3/21/13:
After evaluation and analysis of all dissolution data for the registration batches, the dissolution specifications for the 2 and 8 hour time points for each strength tablet has been updated to reflect dissolution specifications ± 10% as follows:

50 mg tablets:
- *2 hour:* (b) (4)
- *8 hour:* (b) (4)

100 mg tablets:
- *2 hour:* (b) (4)
- *8 hour:* (b) (4)

Level 1, 2, and 3 testing per USP are included in the revised drug product specification sheet.

Reviewer's Assessment of the response: Acceptable.

ALCOHOL DOSE-DUMPING:
The effect of different concentrations of alcohol on the dissolution of both the 50 mg and 100 mg desvenlafaxine tablets was studied in 0.1N HCl and in 0.9% NaCl.

Figure 10 Effect of Alcohol (50mg in 0.1N HCl)

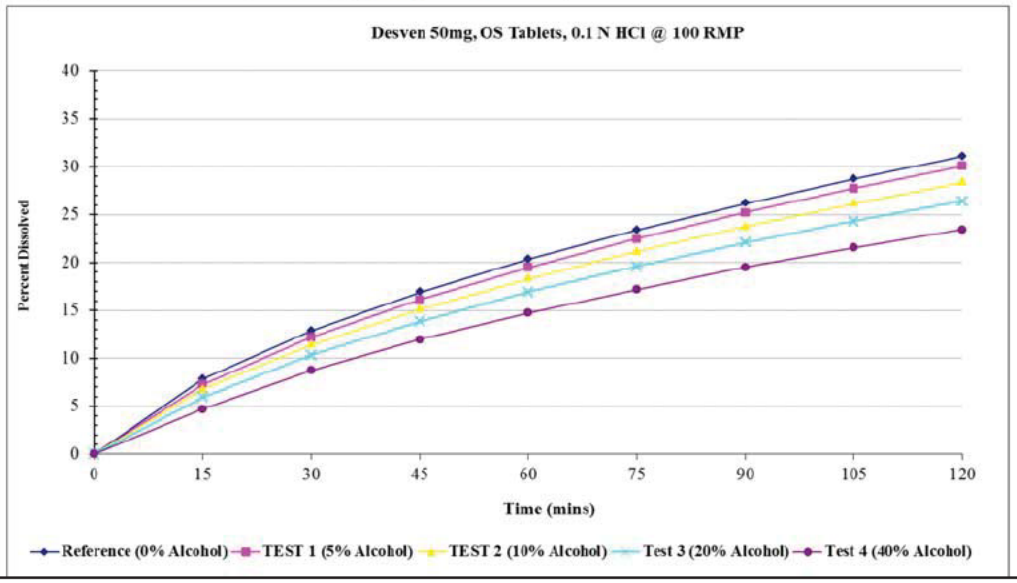


Figure 11 Effect of Alcohol (100mg in 0.1N HCl)

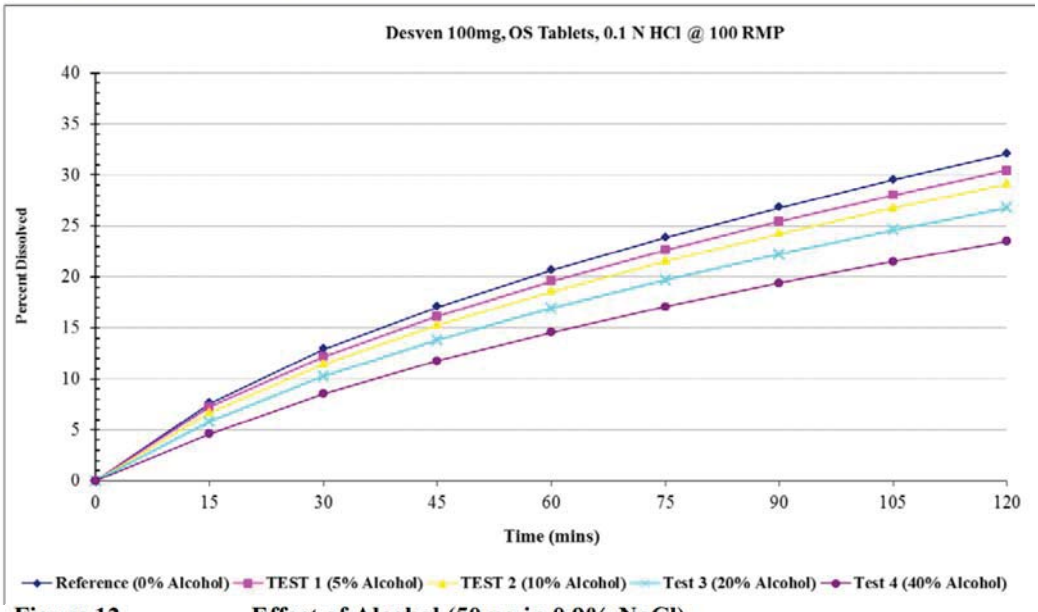


Figure 12 Effect of Alcohol (50mg in 0.9% NaCl)

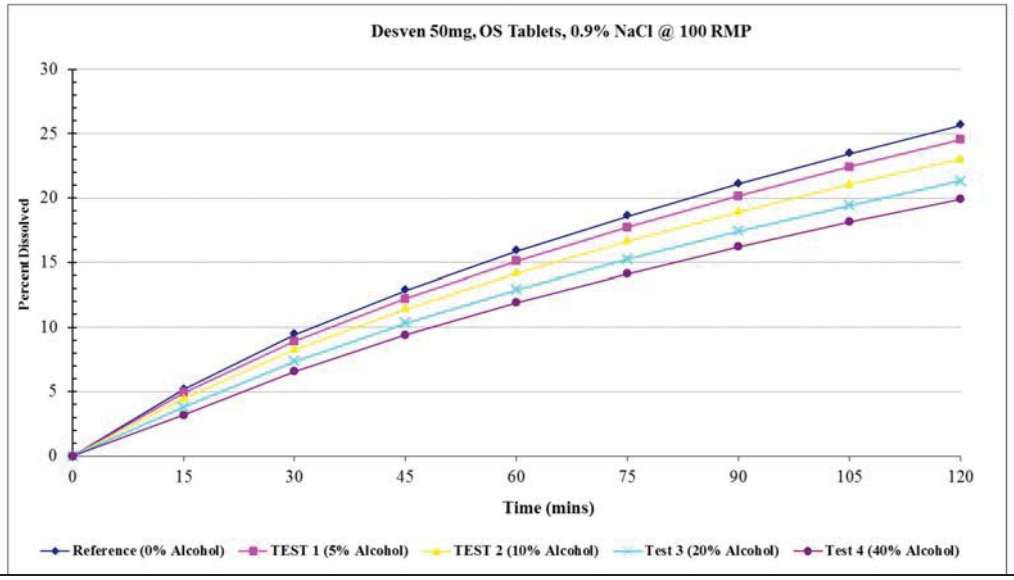
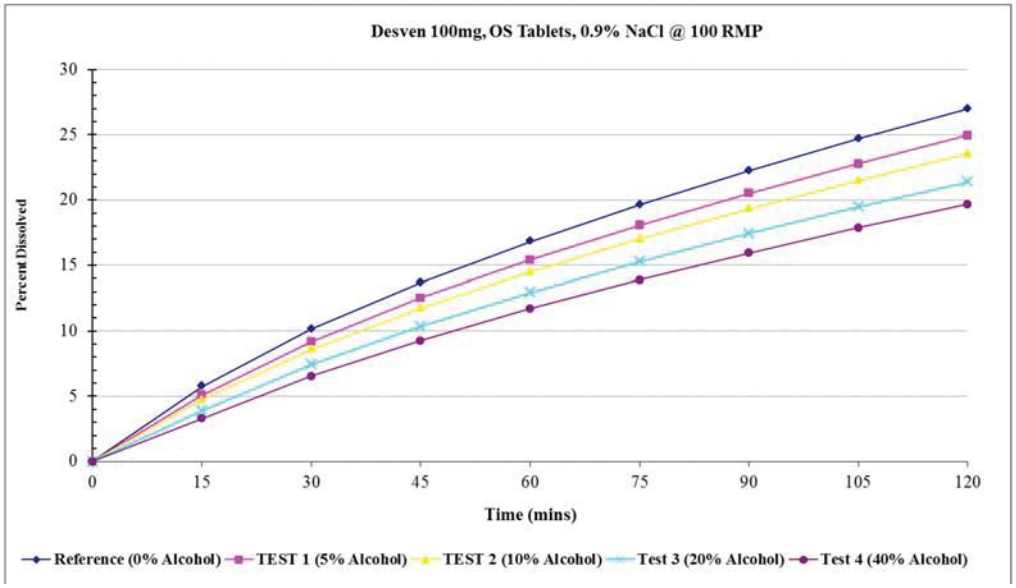


Figure 13 Effect of Alcohol (100mg in 0.9% NaCl)



Reviewer's Assessment of the alcohol dose-dumping study:

The graphs demonstrate that the drug does not dose-dump in vitro with alcohol compared to without alcohol. The general trend for both strengths whether in 0.1 N HCl or 0.9% NaCl is that the drug release is slower with alcohol than without alcohol and the release rate decreases with the increase in alcohol.

EXTENDED RELEASE CLAIM:

The proposed 50 mg and 100 mg tablets are bioequivalent to the approved 50 mg and 100 mg Pristiq® extended release tablets, and both products have a comparable half life of 9-10 hours. Therefore, the extended release claim for the proposed drug product is acceptable.

(b) (4)

Figure 11 Effect of Alcohol (100mg in 0.1N HCl)

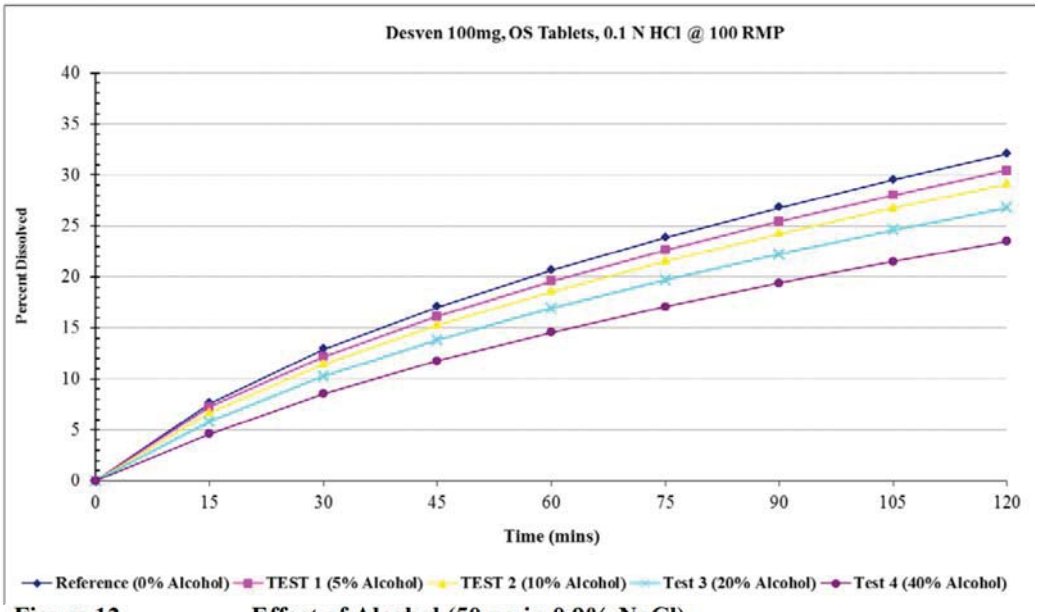
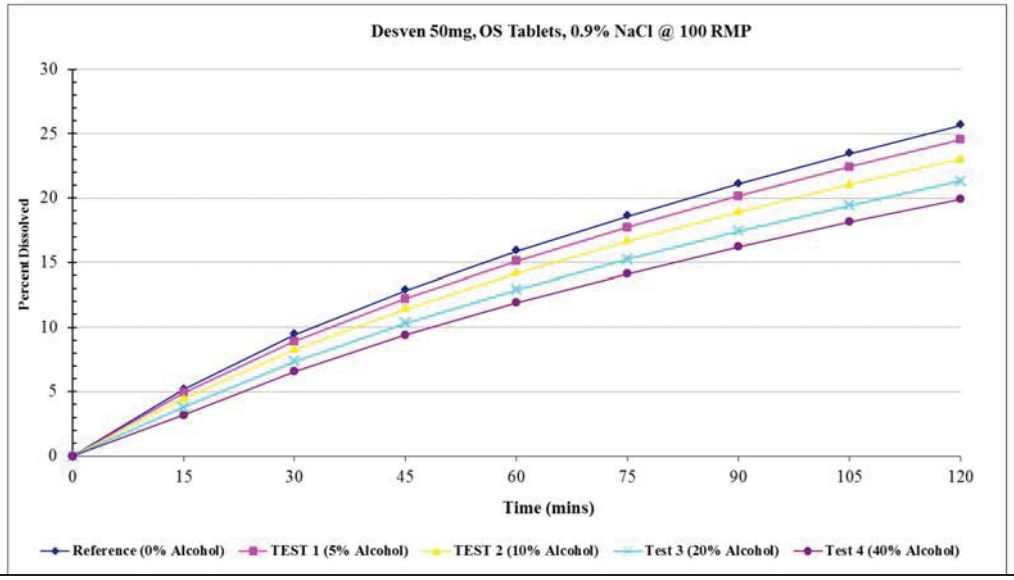


Figure 12 Effect of Alcohol (50mg in 0.9% NaCl)



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Reference ID: 3306579

(b) (4)

Reviewer's final Assessment of the response: Acceptable.

RECOMMENDATION:

- The applicant's dissolution method and acceptance criteria, as summarized below are acceptable by the Agency:

  Dissolution method:
  USP Apparatus I (basket)
  Temperature: 37°C
  Rotation speed: 75 rpm
  Medium: 900 mL 0.9% NaCl in water

  Dissolution acceptance criteria:
  Based on the dissolution data provided, the following dissolution acceptance criterion is acceptable:

  50 mg tablet: Hour 2: (b) (4)%
  Hour 8: (b) (4)%
  Hour 12: NLT (b) (4)%

  100 mg tablet: Hour 2: (b) (4)%
  Hour 8: (b) (4)%
  Hour 12: NLT (b) (4)%

- Alcohol dose-dumping:
  The Applicant has provided data to indicate that dose-dumping does not occur in vitro.

- Extended release claim:
  The extended release claim for the proposed drug product is acceptable.

- (b) (4)

From the Biopharmaceutics perspective, NDA 204683 for Khedezla (desvenlafaxine) Extended Release Tablets (50 and 100 mg/tablet) is recommended for **APPROVAL**.

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/s/

ELSBETH G CHIKHALE
05/09/2013

ANGELICA DORANTES
05/09/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**204683**	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	**I**	**Generic Name**	**Desvenlafaxine (base)**
Medical Division	DPP	**Drug Class**	**SNRI**
OCP Reviewer	**Kofi Kumi**	**Indication(s)**	**Treatment of Major Depressive Disorder**
OCP Team Leader	**Hao Zhu**	**Dosage Form**	**Extended Release Tablets (50mg and 100 mg)**
Pharmacometrics Reviewer		**Dosing Regimen**	**50 mg daily**
Date of Submission	**9/13/2012**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**6/8/13**	**Sponsor**	**Osmotica Pharmaceutical**
Medical Division Due Date	**6/22/13**	**Priority Classification**	**Standard**
PDUFA Due Date	**7/13/13**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Summary

The sponsor has developed a desvenlafaxine base Extended Release (ER) and is seeking approval via the 505(b)(2) route. The sponsor is cross referencing Pristiq (Desvenlafaxine Succinate) ER by Wyeth, which is approved for major depressive disorder. The dosing in MDD for Pristiq is 50 mg daily. The sponsor has developed a 50 and 100 mg ER tablets. Pristiq is also available in 50 mg and 100 mg ER tablets. Clinical studies for Pristiq were conducted using doses from 50 to 400 mg tablets. There is no clinical advantage of the higher doses over the 50 mg dose.

The NDA is dependent on 3 bioequivalent studies:

Study C10-2062: A randomized, open label, two treatment, two treatment, two sequence, single dose, crossover, oral comparative bioavailability study of Desvenlafaxine Extended Release Tablets 50 mg of Osmotica Kft and Pristiq Extended Release Tables 50 mg of Wyeth Pharmaceuticals in healthy, adult, human subjects under fasting condition

Study-VIN-478: A randomized, open label, two treatment, two period, two sequence, single dose, crossover, oral comparative bioavailability study of Desvenlafaxine Extended Release Tablets 100 mg of Osmotica Kft and Pristiq Extended Release Tablets 100 mg of Wyeth Pharmaceuticals Inc in healthy adult human subjects under fasting conditions

Study-VIN-479: A relative bioavailability study of Desvenlafaxine 100 mg ER tablets versus Pristiq 100 mg ER Tablets under fed conditions

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	**505 (b)(2)**			
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**	**3**		
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**	**3**		**Bioanalytical Reports**
I. Clinical Pharmacology	**x**			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**x**			
Healthy Volunteers-				
single dose:	**x**	**3**		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	3			

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?				x

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Reviewing Clinical Pharmacologist	Kofi Kumi, Ph.D.	Date 10/24/12
Team Leader/Supervisor	Hao Zhu, Ph.D.	Date

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/s/

KOFI A KUMI
11/08/2012

HAO ZHU
11/08/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204683
Submission Date	9/13/12
Product name, generic name of the active	(b) (4) (desvenlafaxine)
Dosage form and strength	ER tablets - 50 mg/tablet and 100 mg/tablet
Route of Administration	Oral
Applicant	Osmotica Kereskedelmies Szolgaltato Kft
Clinical Division	Division of Psychiatry Products
Type of Submission	Original NDA – 505(b)(2)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Acting Team Leader	Sandra Suarez, 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		
2.	Is the dissolution test part of the DP specifications?	x		Proposed method: Apparatus 1 (basket), 900 mL of 0.9% NaCl in water at 37 °C, at (b) (4) rpm Proposed acceptance criteria: · 2 hour: (b) (4) % · 8 hours: (b) (4) % · (b) (4)
3.	Does the application contain data to support the proposed dissolution acceptance criteria	x		Section 3.2.P.5.6 Section 3.2.P.8.1
4.	Does the application contain the dissolution method development report?	x		Section 2.7.1
5.	Does the application contain data on the discriminating ability of the dissolution method		x	Data to show the discriminating ability of the dissolution method need to be requested.
6.	Is there a validation package for the analytical method and dissolution methodology?	x		Section 3.2.P.5.3
7.	Does the application include a biowaiver request?		x	Not needed
8.	Does the application include an IVIVC model?		x	Not applicable

Reference ID: 3214584

9.	Is information such as BCS classification mentioned, and supportive data provided?		x	Not applicable
10.	Is information on mixing the product with foods or liquids included?		x	Not applicable
11.	Is there any in *vivo* BA or BE information in the submission?	x		Relative bioavailability studies of the proposed 50 and 100 mg ER tablet versus the RLD 50 and 100 mg ER tablet were conducted. The studies will be reviewed by OCP.
12.	Does the application include in *vitro* alcohol interaction studies?	x		Section 2.7.1

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
13.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
14.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable
15.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable
16.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	See information request for 74 day letter

Biopharmaceutics information request for 74 day letter:

- Provide solubility data for desvenlaxavine (b) (4) across the physiological pH range.
- Provide the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the proposed dissolution method.
- Provide a proposed drug release mechanism for your drug product with supporting data if available.

{See appended electronic signature page}

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

11/8/12
Date

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

{See appended electronic signature page}

Sandra Suarez, Ph.D. 11/8/12
Biopharmaceutics Acting Team Leader Date
Office of New Drug Quality Assessment

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/s/

ELSBETH G CHIKHALE
11/08/2012

SANDRA SUAREZ
11/08/2012