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APPLICATION NUMBER:

204683Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA, 505(b)(2)
Application Number(s) NDA 204863
Priority or Standard Standard

Received Date(s) September 13, 2012
PDUFA Goal Date July 13, 2013
Division / Office ONDI/DPP

Reviewer Name(s) Roberta Glass, M.D.
Review Completion Date June 3, 2013

Established Name Desvenlafaxine ER
(Proposed) Trade Name Khedezla
Therapeutic Class Selective Serotonin and Norepinephrine
Reuptake Inhibitor (SNRI)
Applicant Osmotica Pharmaceutical Corporation

Formulation(s) 50 mg and 100 mg Tablet,
Extended Release (ER)
Dosing Regimen 50 mg qd
Indication(s) Major Depressive Disorder
Intended Population(s) Adult

I. Introduction and Regulatory Background

The active ingredient for this 505(b)(2) NDA application is **desvenlafaxine (base)**; this drug product has been given permission to have the proprietary name of **Khedeza[®] ER** (FDA letter to the sponsor: 4 /24/13). Khedeza[®] ER is designed to be bioequivalent to the marketed product **Pristiq[®] ER** (NDA 21-992: desvenlafaxine succinate). Pristiq[®] ER is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), was first marketed in February, 2008, and is approved for the indication of Major Depressive Disorder in adults with a recommended dose of 50 mg qd.

Osmotica Pharmaceuticals, the sponsor of Khedeza[®] ER, first discussed their interest in submitting this 505(b)(2) NDA submission in a meeting with FDA in November, 2011. They submitted their protocols for bioequivalence studies under IND 111073. Of the 3 bioequivalence studies submitted for review in this 505(b)(2) application, one was conducted in the USA, one in Hungary and one in India. Khedeza[®] ER (desvenlafaxine, base) will be available in 50 mg and 100 mg extended release tablets, as is Pristiq[®]ER.

II. Materials Reviewed

NDA Submission dated: 9/13/12

Study Report C10-2062 (a.k.a.OS230-1006 & S11-0011)

Study Report 11-VIN-478

Study Report 11-VIN-479

Summary of Clinical Data

Proposed Labeling

Financial Disclosure Certification

FDA Reviews for NDA 204683

Clinical Pharmacology Review: Kumi (5/31/13)

Pharmacology/Toxicology Review: Mathew (5/29/13)

Chemistry Review: Shironmai (5/13/13)

Biopharmaceutics Review: Chilchale (5/9/13)

Office of Scientific Investigations (5/7/13)

Patient Labeling Review: Griffiths (5/17/13)

Propriety Name Review: Holmes (4/24/13)

Meeting Minutes: IND 11073 dated 11/4/11

III. Financial Disclosures

Form 3434 (Certification of Financial Interests and Arrangements of Clinical Investigators), signed and dated on August 31, 2012 by the Managing Director of

Clinical Review
NDA 204683, 505 (b)(2)
Roberta Glass, M.D.

Osmotica Kft, states that no clinical investigators listed in this NDA benefited from any financial arrangement based on study outcome, or received significant payments of other sorts from the sponsor of the NDA.

IV. Chemistry Manufacturing and Controls

The CMC submissions for this application were determined to be adequate and acceptable. There are no CMC pending issues. However, the CMC review cites that a site inspection is still pending, and is required for a complete recommendation for approval from the CMC perspective. Please refer to the chemistry review for more details (Bhamidipati and Shironmani: 5/13/13).

V. Preclinical Pharmacology/Toxicology

There were no new pharmacology or toxicology studies submitted in with this NDA. All non-clinical data is based on findings for Pristiq[®]. The Pharmacology/Toxicology review states that no impurities, degradants, or novel excipients in the desvenlafaxine (base) extended release tablets have been identified; therefore, no new toxicology studies are required at this time. Please see the Pharmacology/toxicology Memo to the File for further details (Mathew: 5/29/13).

VI. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review (Kumi: 5/31/13) concluded that Khedezla[®] is bioequivalent to Pristiq[®] at both strengths of 50 mg and 100 mg under fasting conditions, that Khedezla[®] is bioequivalent to Pristiq[®] 100 mg under fed conditions and that Khedezla[®] can be administered with or without food. Khedezla[®] median Tmax was later when the study was conducted under fed conditions, but the reviewer did not expect this difference to be clinically relevant. There are no post-marketing studies recommended, and OCP recommends approval of Khedezla[®] at the same dosing recommendations approved for Pristiq[®].

The OCP review (Kumi: 5/31/13) presents the following summary tables comparing 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

Clinical Review
 NDA 204683, 505 (b)(2)
 Roberta Glass, M.D.

Parameters	Geometric Least Squares Means (N=35)		(T/R) %	90% CI
	Reference (R)	Test (T)		
C _{max} (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
T _{max} * (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)		
C _{max}	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
T _{max} *	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)		
C _{max}	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
T _{max} *	7.00 (4 -24)	6.00 (3 – 14)	NA	NA

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

The Biopharmaceutics Review (Chikhale: 5/9/13) concluded that the dissolution method and acceptance criteria are acceptable. It was also concluded that the sponsor had provided sufficient data to indicate that dose-dumping with alcohol does not occur in vitro. The review also stated that the extended release claim of the Khedezla was found to be acceptable. This review recommended approval of this application.

Please see the OCP review (Kumi: 5/31/13) and the Biopharmaceutics Review (Chikhale: 5/9/13) for further details.

VII. Review of Clinical Safety Data

A. Summary Table of Clinical Trials

All clinical studies conducted in this NDA were bioequivalent (relative bioavailability to Pristiq) studies. There were no efficacy or safety studies conducted under this NDA. The following table summarizes the 3 open label studies submitted in this NDA.

Study	Design/Dose	Subjects
C10-2062 (OS230-1006 & S11-0011)/USA	Open label, two-way, crossover, single dose bioequivalence in <i>fed</i> state: Khedezla ER 100 mg to Pristiq ER 100 mg	N=36 healthy adults Completed: N=33
11-VIN-478 Hungary	Open label, two-way crossover, single dose bioequivalence in <i>Fasting</i> state of Khedezla ER 50 mg and Pristiq ER 50 mg	N=42 healthy adults Completed: N=38 (12 female; 26 male).
11-VIN-479/ India	Open label, two-way crossover, single dose bioequivalence in <i>fasting</i> state of Khedezla ER 100 mg and Pristiq ER 100 mg.	N=42 healthy adults Completed: N=35 (12 female; 23 male).

B. Demographics of clinical trials

There have been a total of 106 individuals exposed to a single dose of Khedezla. The majority of subjects are male (66%) with a mean age of 32 years old, and an age range of 18-64.

C. Study Summaries

Protocol C10-2062 (also named OS230-1006 & S11-0011)

This study (USA) is an open-label, inpatient, 24 hour, single dose, randomized, two-period, two treatment crossover study in **fed** conditions. Single doses of desvenlafaxine 100 mg ER and single doses of Pristiq 100 mg were administered with a 7 day wash out period. Blood samples were obtained at 90 minutes pre-dose, post-dose times at 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. Protocol calls for 36 healthy adults 18-55 y.o. with weight \geq 110 lbs, and BMI of 17.5 to 32.4 kg/m². Screening included history and physical, ECG, routine labs, urinalysis, UDS, breath alcohol test, pregnancy test, and Columbia Suicide Severity Rating Scale (CSSR).

Monitoring during the study included vitals (seated). Laboratory tests, vitals and CSSR were repeated at study termination.

Results

The study was completed by 33 subjects which included 15 females and 21 males with a mean age of 35.2 yo (range 20-53). Demographics reported that 52.78% were Caucasian, 41.67% African Americans, 2.78% Asian, and 2.78% other. The following sponsor table summarizes the demographics for this study:

Demographics for Study C10-262 (Table excerpt from sponsor's Clinical Study Report p.37)

Parameter	All Subjects ¹ N = 33	Females ¹ N = 13	Males ¹ N = 20
Age (range)	35.3 (20 - 53)	37.3 (23 - 53)	34.1 (20 - 52)
Weight [lbs] (range)	175.7 (114.6 - 235.0)	155.2 (114.6 - 190.0)	189.1 (136.8 - 235.0)
Height [in.] (range)	67.9 (61.5 - 73.9)	64.7 (61.5 - 67.0)	70.1 (62.3 - 73.9)
BMI (range)	26.6 (20.4 - 32.3)	26.0 (20.4 - 32.3)	27.1 (21.8 - 32.1)
Race [N(%)]			
Asian:	1 (3.0%)	-	1 (5.0%)
African American:	14 (42.4%)	4 (30.8%)	10 (50.0%)
White:	17 (51.5%)	9 (69.2%)	8 (40.0%)
White, American Indian or Alaskan Native:	1 (3.0%)	-	1 (5.0%)

¹Subjects used in final statistical results.

No serious adverse events (AEs) were reported. One subject (021) discontinued due to an adverse event of vomiting which was considered to be probably related to study drug treatment. The most common AEs reported were nausea (4/6 or 11.11%), headache (3/36 or 8/33%), and vomiting (2/36 or 5/56%). No clinically significant laboratory changes were noted by the sponsor in the study report. Three subjects did not take both study drugs and were not included in the final bioavailability calculations. The following sponsor table summarizes the adverse events noted.

Adverse Events for Study C10-262 (Table excerpt from sponsor's Clinical Study Report p.44)

Adverse Event (AE) MedDRA SOC / Preferred Term ⁺	Treatment Arm	
	Test Product A: Desvenlafaxine 100 mg ER Tablets N = 35	Reference Product B: Pristiq 100 mg ER Tablets N = 34
Gastrointestinal disorders		
Nausea	2 (5.71%)	2 (5.88%)
Vomiting	1 (2.86%)	1 (2.94%)
Nervous system disorders		
Headache	3 (8.57%)	-

Protocol 11-VIN-478

This study, conducted in Budapest, Hungary, is a randomized, open label, two period, single dose, crossover, oral comparative bioavailability study of 50 mg desvenlafaxine ER tables and 50 mg Pristiq ER tablets in **fasting** condition in healthy adult humans aged 18-45 yo. Screening included history and physical, chest X-ray, ECG, routine labs, serum pregnancy test, UDS, and alcohol breath test. Vitals (seated) were monitored during the study. Laboratory tests and vitals were repeated at study termination.

Results

The study was completed by 38 subjects (14 female, 28 male), with a mean age of 28.9 y.o. and a range 19-42. No serious adverse events were reported. Adverse events included vomiting (3/36 or 8%), and increased serum bilirubin (1/36 or 3%). The sponsor table below summarizes these adverse events.

Adverse Events for Study 11-VIN-478 (Table excerpt from sponsor's Clinical Study Report p.54)

Subject Number	Adverse event	Time and Date of event	Investigational Product (Reference (R) /Test (T))	Relation to the investigational product
03	C/o vomiting, single episode, containing food particles. No other associated complaints.	12:20, 25 Jun 2012	T	Possible
37	C/o vomiting, single episode, containing food particles. No other associated complaints.	12:36, 25 Jun 2012	R	Possible
04	C/o vomiting, single episode, containing water and saliva. No other associated complaints.	10:10, 02 Jul 2012	T	Possible
22	Increased serum bilirubin (Increased Bilirubin Total (3.10 mg/dl), Bilirubin conjugated (0.53 mg/dl), Bilirubin	NA	T	Possible

Protocol 11-VIN-479

This study, conducted in India, is a randomized, open label, two period, single dose, crossover, oral comparative bioavailability study of 100 mg desvenlafaxine ER (Khedezla) tablets and 100 mg Pristiq ER tablets in **fasting** condition in healthy adult humans aged 18-45 yo. Screening included history and physical, chest X-ray, ECG, routine labs, serum pregnancy test, UDS, and alcohol breath test. Vitals (seated) were monitored during the study. Laboratory tests, pregnancy test, physical, and vitals were repeated at study termination.

Results

The study enrolled 42 subjects (14 female, 28 male), with a mean age of 31 y.o. and a range 18-45. No serious adverse events were reported. The study was completed by 35 subjects (12 females and 23 males).

Adverse events included vomiting (6/35 or 17%) and giddiness (1/35 or 3%). Laboratory changes of note included decrease hemoglobin count (7/35 or 20%) and one case of elevated SGPT (Subject 33: baseline; 24.23 U/L; termination: 50.67 U/L; normal range: 0-40 U/L).

The sponsor table below summarizes the adverse events. (from Study report pp. 59-60)

Clinical Review
 NDA 204683, 505 (b)(2)
 Roberta Glass, M.D.

Subject Number	Adverse event	Time and Date of event	Investigational Product (Reference (R) /Test (T))	Relation to the investigational product
30 (period 01)	C/o vomiting, single episode, containing water and saliva. No other associated complaints.	11:20, 29 Jun 2012	T	Possible
04 (period 01)	C/o Giddiness. No other associated complaints.	13:11, 29 Jun 2012	T	Possible
	C/o vomiting, single episode, containing food particles. No other associated complaints.	13:34, 29 Jun 2012		Possible
36 (period 02)	C/o vomiting, single episode, containing water and saliva. No other associated complaints.	10:10, 06 Jul 2012	R	Possible
15 (period 02)	C/o vomiting, single episode, containing water and saliva. No other associated	11:04, 06 Jul 2012	R	Possible
	complaints.			
14 (period 02)	C/o vomiting, single episode, containing water and saliva. No other associated complaints.	11:31, 06 Jul 2012	T	Possible
26 (period 02)	C/o vomiting, single episode, containing water and saliva. No other associated complaints.	12:30, 06 Jul 2012	R	Possible

Summary table of laboratory changes

Sub. No.	Lab Parameters	Advice	Follow up	Ongoing/completed
01	Hb - Low	Tab. Livogen twice daily for 15 days.	After 15 days with reports of re-test	completed

Sub. No.	Lab Parameters	Advice	Follow up	Ongoing/completed
03	Hb - Low	Tab. Livogen twice daily for 15 days.	After 15 days with reports of re-test	completed
09	Total Count - high	Repeat	After 04 days with reports of re-test	completed
10	Total Count - high	Repeat	After 04 days with reports of re-test	completed
11	Hb - Low	Tab. Livogen twice daily for 15 days.	After 15 days with reports of re-test	Ongoing
14	Hb - Low	Tab. Livogen twice daily for 15 days.	After 15 days with reports of re-test	completed
	Total Count -high	Repeat	After 04 days with reports of re-test	
17	Eosinophil – high	Tab Cetirizine (10mg) once daily for 05 days.	After 05 days with reports of re-test	completed
18	Eosinophil – high	Tab Cetirizine (10mg) once daily for 05 days.	After 05 days with reports of re-test	completed
20	Hb - Low	Tab. Livogen twice daily for 15 days.	After 15 days with reports of re-test	completed
23	Hb - Low	Tab. Livogen twice daily for 15 days.	After 15 days with reports of re-test	completed
25	Eosinophil – high	Tab Cetirizine (10mg) once daily for 5 days.	After 05 days with reports of re-test	completed
29	Total Count - high	Repeat	After 05 days with reports of re-test	completed
32	Hb - Low	Tab. Livogen twice daily for 15 days.	After 15 days with reports of re-test	completed
33	SGPT- High	Rest, Low fat with high carbohydrate diet.	After 07 days with reports of re-test	Ongoing
38	Total Count - high	Repeat	After 04 days with reports of re-test	completed
	Eosinophil – high	Tab Cetirizine (10mg) once daily for 5 days.	After 05 days with reports of re-test	

Sub. No.	Lab Parameters	Advice	Follow up	Ongoing/completed
40	Total Count - high	Repeat	After 04 days with reports of re-test	completed

VIII. Inspections

The Division of Bioequivalence and GLP Compliance/Office of Scientific Investigations (please see review by Jyoti B. Patel, PhD: 5/7/13) inspected select data from all 3 studies conducted in USA, Hungary, and India. The review concluded that all data

investigated was acceptable for further agency review. Please see the review for further details (Patel: 5/7/13).

IX. Pediatric Plan

When Pristiq[®] was approved in 2007, the sponsor was requested to conduct a post marketing study safety and efficacy study in the pediatric population with MDD. (b) (4)
PeRC met with the division on May 29, 2013, and it was discussed that any pediatric studies required to be conducted under this NDA for Khedezla[®] be deferred (b) (4)

A full waiver for doing pediatric studies in children less than 7 years old was granted at the PeRC meeting on May 29, 2013, as there are difficulties in the diagnosis and recruitment of MDD in this young pediatric population.

X. Conclusions and Recommendations

All FDA disciplines have concluded that the sponsor has submitted sufficient data to show that Khedezla[®] ER is bioequivalent to the marketed product Pristiq[®] ER. Although the clinical exposure of Khedezla[®] ER is small, the active ingredient desvenlafaxine has been marketed since 2008 and has an acceptable safety profile. Therefore, an approval action is recommended.

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/s/

ROBERTA L GLASS
06/03/2013

JING ZHANG
06/04/2013