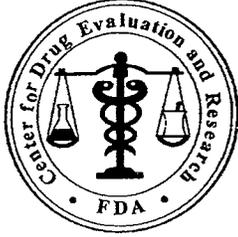


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-992

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 20, 2008

To: Thomas Laughren, MD, Director
Division of Psychiatry Products

Thru: Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Division Director
Division of Medication Errors and Technical Support (DMETS)

From: Todd Bridges, RPh, Team Leader
Division of Medication Errors and Technical Support (DMETS)

Subject: Label and Labeling Review

Drug Name(s): Pristiq (Desvenlafaxine Succinate) Extended-Release Tablets
50 mg and 100 mg

Application Type/Number: NDA 21-992

Applicant/sponsor: Wyeth Pharmaceuticals

OSE RCM #: 2008-302

1 INTRODUCTION

This memorandum is in response to a January 15, 2008, request from the Division of Psychiatry Products for a review of the revised labels and labeling submitted by the applicant in response to OSE Review #2007-2197, dated January 15, 2008.

2 MATERIAL REVIEWED

Revised container labels and carton labeling which were submitted by the applicant on February 14, 2008. (see Appendices A through D)

3 DISCUSSION

DMETS acknowledges that the sponsor has addressed all of our label and labeling recommendations.

4 CONCLUSIONS

We have no additional comments at this time.

If you have any questions or need clarifications, please contact Daniel Brounstein, OSE Project Manager, at (301) 796-0674.

4 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

∞ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

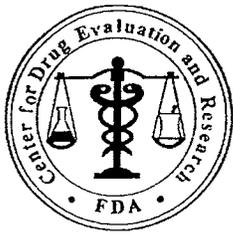
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/s/

Todd Bridges
2/20/2008 10:45:30 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/20/2008 12:34:33 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 5, 2008

To: Thomas Laughren, M.D., Director
Division of Psychiatry Products

Through: Jodi Duckhorn, M.A., Team Leader
Patient Labeling and Education Team
Division of Risk Management (DRM)

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Patient Labeling and Education Team
Division of Risk Management

Subject: DRM Review of Patient Labeling (Medication Guide)

Drug Name(s): Pristiq (desvenlafaxine) Extended-Release Tablets, oral

Application Type/Number: N21-992

Applicant/sponsor: Wyeth Pharmaceuticals Incorporated

OSE RCM #: 2007-2200

INTRODUCTION

Wyeth submitted a New Drug Application (NDA) #21-992 for Pristiq (devenlafaxine) Extended-Release Tablets on December 22, 2005 for the treatment of Major Depressive Disorder (MDD). The Agency took an Approvable action on January 22, 2007 for this NDA, citing deficiencies in the areas of Chemistry, Manufacturing and Controls, RiskMAP Evaluation Activities, need for Post Marketing Commitments, and issues related to the cartons and containers.

The sponsor submitted a Completed Response to the January 22, 2007 Approvable letter on August 29, 2007. The submission includes a revised draft labeling, RiskMAP and Medication Guide.

MATERIAL REVIEWED

- Review Division revised PI dated January 31, 2008 and February 4, 2008.
- Medication Guide dated January 31, 2008.

DISCUSSION

The purpose of Medication Guides is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor has a Flesch Kinkaid grade level of 10.2 and a Flesch Reading Ease score of 48. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). Our revised MG has a Flesch Kinkaid grade level of 7.6 and a Flesch Reading Ease score of 60.5%.

In our review of the MG, we have:

- simplified wording where possible,
- made it consistent with the Professional Information,
- removed unnecessary or redundant information
- ensured that the Medication Guide follows the approved Antidepressant template and incorporates appropriate additional information.
- ensured that the Medication Guide meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

CONCLUSIONS AND RECOMMENDATIONS

- The sponsor must comply with all of the Medication Guide Regulations as specified in 21 CFR 208. Specifically:

- the sponsor should clarify how they intend to distribute the Medication Guide for Pristiq. Unless the Medication Guide is packaged with the product in unit-of-use packaging, patients are unlikely to receive the Medication Guide.
- we are unable to locate carton and container labels in the EDR. 21CFR 208.24 (d) states: "The label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner."
- Since information has been added to the template antidepressant Medication Guide to make it product-specific for Pristiq, the sponsor may not use the tear-off sheet that is shared by other anti-depressant drugs for distribution of the Pristiq Medication Guide. This change will require that the sponsor ensure that every patient receives the Pristiq product-specific Medication Guide and follow 21 CFR 208.24 (e) which states:
 - “Each authorized dispenser of a prescription drug product for which a Medication Guide is required under this part shall, when the product is dispensed to a patient (or to a patient’s agent), provide a Medication Guide directly to each patient (or to the patient’s agent) unless an exemption applies under §208.26.”
- The sponsor uses the terms “doctor” and “healthcare professional” in the Medication Guide. The term “healthcare professional is too vague and should not be used in patient materials. Use either “healthcare provider” or “doctor” consistently throughout the Medication Guide, not both.
- The bullet which explains major depressive episode, according to the DSM IV criteria, is highly technical and inappropriate to include in patient materials. Patient materials should be written at a 6th to 8th grade reading level. This type of information is more appropriate for healthcare providers than patients.
- Information on the signs and symptoms of serotonin syndrome as well as instructions to seek medical care ~~_____~~ “What are the possible side effects of Pristiq.”
- In the last paragraph under the section, “What are the possible side effects of Pristiq, the last statement has been added to the Medication Guide in accordance with the January 3, 2008 Interim Final Rule for the Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products. It is a verbatim statement that applies to the Medication Guide Regulations 21CFR 208.20 (b) (7) (iii) for drugs approved under section 505 of the act.

Please let us know if you have any questions.

19 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Sharon Mills
2/5/2008 02:08:48 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
2/5/2008 02:17:35 PM
CSO

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: January 17, 2007

TO: Thomas Laughren, M.D., Director
Division of Psychiatry Products, HFD-130

THROUGH: Ellis Unger, MD, Deputy Director (Acting)
Office of Surveillance and Epidemiology (OSE), HFD-400

FROM: OSE Venlafaxine/Desvenlafaxine Risk Management Program
Review Team

DRUG: Venlafaxine (Effexor & Effexor XR); 20-151, 20-699

Desvenlafaxine Extended Release tablets (proposed proprietary
name Pristiq); 21-992,

APPLICANT: Wyeth Research

SUBJECT: Risk Management Plans, dated March 6, 2006, May 25, 2006, and
June 9, 2006

RCM #: 2006-665, 2006-671

1 EXECUTIVE SUMMARY

This consult follows a request from the Division of Psychiatry Products (DPP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the Risk Management Plans (RMPs) for venlafaxine and desvenlafaxine.

Venlafaxine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant approved by the FDA for the treatment of major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder. Desvenlafaxine is a major active metabolite of venlafaxine and is currently under review in DPP and the Division of Reproductive and Urologic Products (DRUP) being proposed for the treatment Major Depressive Disorder (MDD) and vasomotor symptoms (VMS) associated with menopause.

In the postmarketing setting, venlafaxine has been found to be associated with worse outcomes from overdose, compared to selective serotonin reuptake inhibitors (SSRIs).

The safety profile of desvenlafaxine in clinical trials has appeared similar to that of venlafaxine.

The sponsor has implemented several risk management strategies to address the risks of overdose toxicity with venlafaxine. They have added language to the venlafaxine label to inform health care practitioners about findings from the postmarketing epidemiologic studies that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. The sponsor has also implemented an education program for clinicians and patients to guide appropriate use of antidepressants in high-risk patients. Finally, they have implemented a smaller unit-of-use packaging to facilitate more frequent patient contact and to help reduce the risks associated with overdose. These risk management strategies were conveyed to the healthcare community via a "Dear Health Care Provider Letter" on October 17, 2006. The Sponsor's proposal risk management strategy is similar for desvenlafaxine; however, details of the Sponsor's educational plan were not provided in their RMP submission.

We have concerns that this risk management strategy may not go far enough in reducing the overdose risks. Although there is some evidence that smaller packs coupled with blister packing have reduced suicides in other countries, we are not optimistic that this strategy will succeed in the U.S. The proposed voluntary smaller pack is not supported by labeling, and does not fit with usual medication insurance practices. Such packaging may not be adopted by generic companies. Moreover, use of the smaller pack would only have a potential impact on patients who impulsively commit suicide. Patients who plan suicide would be able to stockpile drug, irrespective of whether smaller packs are implemented.

The Division may need to consider additional approaches to minimize this risk, including consideration for reservation of venlafaxine and desvenlafaxine as second-line therapy. Verispan data indicate that the use of venlafaxine has increased overall in the past 10 years, and the proportion of prescriptions by non-psychiatrists has also increased. Use data also indicate that venlafaxine is being used as a first line antidepressant drug in up to 60% of prescriptions written. In order to minimize the risks of overdose toxicity and sustained hypertension, the Division and Sponsor should consider ways to minimize exposure, including limiting the MDD indication for venlafaxine and desvenlafaxine to patients who have not benefited from less toxic antidepressants.

If the Division is not prepared to take this approach at this time, we recommend the Sponsor be required to evaluate comprehensively the risk management strategies described in their submissions on overdose toxicity and suicide. They should provide additional details on their risk management strategies, in particular, specifics on how the smaller pack is being implemented. The risk management strategies (including labeling) for desvenlafaxine should be the same as those for venlafaxine, as the risk profiles are expected to be the similar post-marketing. We have provided specific comments, questions, and recommendations on the various components of the RMP to convey to the Sponsor in section 4.1 of this review.

2 BACKGROUND

2.1 *Venlafaxine*

Venlafaxine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant indicated for the treatment of major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder. Venlafaxine is available as Effexor Immediate Release Tablets, approved for marketing in the U.S. on December 28, 1993 and Effexor XR Extended Release Capsules, approved for marketing in the U.S. on October 20, 1997. Generic versions of the immediate release venlafaxine have recently been approved by the Agency. The Teva generic version of venlafaxine received approval on August 3, 2006 and the Mylan generic version of venlafaxine received tentative approval on August 14, 2006.

In December 2004, the Medicines and Healthcare Products Regulatory Agency (MHRA) of the U.K. issued a report noting concerns about the overdose toxicity of venlafaxine and its cardiovascular safety profile. DPP consulted OSE to evaluate whether there was any evidence in the U.S. that venlafaxine overdose is associated with a higher fatality rate than SSRI overdosage. Dr. Andrew Mosholder, M.D., M.P.H. completed his review of overdose toxicity of venlafaxine and other antidepressant drugs in June, 2005,¹ and concluded that available data indicated that venlafaxine overdose was associated with worse outcomes than overdosage with SSRIs (although the outcomes appeared to be less severe than those associated with TCA overdose). Dr. Mosholder recommended in his review that there should be a risk management strategy to communicate the findings and that venlafaxine should be reserved until other less toxic compounds have been tried.

Drs. Lourdes Villalba and Judy Racoosin, Medical Officer and Team Leader, respectively, from the DPP Safety Team conducted an evaluation of the Toxic Exposure Surveillance System (TESS) as a potential source to calculate an overdose fatality rate for venlafaxine and other antidepressants.² Their analysis of rates of overdose fatalities using TESS data as a numerator and Verispan™ data as a denominator was not consistent with previous findings; however, they were not confident in TESS data, believing that there is underascertainment of overdoses and overdose fatalities in TESS.

Dr. Gregory Dubitsky (Clinical Reviewer in DPP) concluded in his review of studies of venlafaxine in overdose that, relative to SSRIs, venlafaxine overdosage is associated with an increased fatality rate in the U.K., and an increased rate of ICU/CCU admission in the U.S. He recommended labeling revisions, and dispensation of no more than 2,100mg of venlafaxine at one time to outpatients judged to be at risk of suicide.³

¹ Mosholder A. Overdose toxicity of venlafaxine and other antidepressant drugs PID D040807; entered into DFS on June 16, 2005.

² Villalba L, Racoosin J. Overdose toxicity with venlafaxine and other antidepressants; entered into DFS on May 22, 2006.

³ Dubitsky G. Review and evaluation of clinical data: toxicity of venlafaxine in overdosage (NDA 20-151 and 20-699), final signature in DFS 10/20/06.

The Sponsor's response to FDA included new data regarding the risk of suicide in patients treated with venlafaxine, based on experience at Kaiser Permanente in Northern California. This study was funded by Wyeth. The objective of this study was to determine whether venlafaxine treatment increased the risk of suicide-related fatality, suicide attempt, or fatal outcome (from overdose and all attempts) compared to fluoxetine, citalopram, or paroxetine. Dr. Dubitsky concluded that the study "...suggests that, in the U.S., venlafaxine-treated patients carry a slightly higher burden of suicide risk factors compared to those treated with citalopram, fluoxetine, and paroxetine." He also stated that the study also suggests that "...venlafaxine-treated patients may be more likely to attempt suicide than those treated with the other three agents but the increased risk is likely to be small and may be biased by residual confounding." OSE has not reviewed this observational study.

In May 2006, the MHRA released a Summary of Basis for Regulatory Position pertaining to venlafaxine overdose toxicity. The summary⁴ included the following regulatory risk minimization proposals:

- A two-week pack should be introduced and considered for initial therapy, dose changes and all patients who are assessed to be at high risk of suicide.
- Because of the increased risk of therapeutic dose/overdose-related toxicity, and the increased risk of suicidal behaviour in severely depressed patients, initiation of doses =300mg should be restricted to specialist care and treatment should be managed under specialist supervision or shared care arrangements.
- Use in those at known very high risk of cardiac arrhythmia and those with uncontrolled hypertension should be contraindicated.
- A warning should be introduced regarding patients with heart disease, which might increase the risk of arrhythmia.
- Concomitant use of SSRIs should only be undertaken on specialist advice.
- Concomitant use of potent CYP3A4 inhibitors (e.g. erythromycin, azoles, protease inhibitors), and drug combinations that inhibit both CYP2D6 and CYP3A4 should only be considered if strictly indicated.
- The patient information leaflet should be updated accordingly, and a headlines section should be introduced, which highlights the advice for patients with suicidal thoughts to seek urgent medical help.
- The new prescribing advice should be communicated in a letter to healthcare professionals.

Dr. Dubitsky concluded in his review that Wyeth's counterproposal for describing information pertaining to overdosage with venlafaxine in labeling appears to be reasonable and DPP requested a supplemental CBE.⁵ The CBE supplement was approved

⁴Available at

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CO N2023843&ssTargetNodeId=389; scroll down and open pdf document entitled "Venlafaxine (Efexor) summary basis for regulatory position.

⁵ NDA 20-151 and 20-699 CBE-0/CBE-30 supplement request letter, 8/10/2006

by DPP on October 20, 2006⁶ and incorporates information pertaining to the studies reviewed.

2.2 *Desvenlafaxine*

Desvenlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI) and is a major active metabolite of venlafaxine. The NDA (21-992) for the proposed indication of MDD was submitted to DPP on December 22, 2005. The NDA _____ for the proposed indication of treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause was submitted to the DRUP on _____

The DPP clinical reviewer, Dr. Robert Levin, found the safety profile of desvenlafaxine to be similar to that of venlafaxine. In the short-term, controlled trials that included a venlafaxine treatment arm, there were no important differences in the safety profiles between the desvenlafaxine and venlafaxine, and there were no unexpected adverse events related to treatment with desvenlafaxine.⁷ However, there were a high proportion of subjects treated with desvenlafaxine who discontinued treatment early in the study due to adverse events that included nausea, vomiting, dizziness, insomnia, headache, asthenia, somnolence, and sweating. Compared to the placebo and venlafaxine groups, desvenlafaxine was also associated with a higher proportion of subjects who developed significant elevations in the hepatic transaminase ALT/SPGT. Significant serum ALT elevations were reported for 0.6%, 0.1%, and, 0% in the desvenlafaxine, placebo, and venlafaxine groups, respectively. In two events classified as serious, the abnormalities resolved upon discontinuing desvenlafaxine treatment. According to the clinical review, the main safety concern with desvenlafaxine treatment is the dose-related risk of hypertension. All of the desvenlafaxine clinical trials were of short duration and the hypertensive events did not appear to be associated with serious cardiovascular, cerebrovascular, renal, or other end-organ damage. However there was concern that desvenlafaxine-induced hypertension could lead to such adverse cardiovascular outcomes with longer treatment.

The Division of Cardiovascular and Renal Products (DCaRP) was consulted for their input and recommendations regarding sustained hypertension with desvenlafaxine treatment. Their analysis of blood pressure changes with desvenlafaxine, venlafaxine, and placebo showed both active drugs to be higher than placebo and BP changes between venlafaxine and desvenlafaxine to be similar, although diastolic BP appeared higher in the supine position for desvenlafaxine. DCRP recommended that the desvenlafaxine label should be similar to the venlafaxine label with regard to this safety concern.⁸

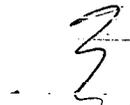
⁶ See NDA 20-151/SLR-045 and 20-699/SLR-072 approval letter, dated 10/20/06.

⁷ Levin R. DRAFT Clinical Review of NDA 21-992 Desvenlafaxine for Major Depressive Disorder, dated 10-10-06.

⁸ Desai M. DCRP Consultative Review of NDA 21-992 Desvenlafaxine; final signature in DFS dated 8/3/06.

The Sponsor identifies the following known and potential risks that require further evaluation:

- QT/QRS interval prolongation – the Sponsor concluded that their studies (preclinical studies, a thorough QT study, and episodic ECG analyses during clinical trials) did not reveal a signal concerning QT interval prolongation, QRS prolongation, or ventricular arrhythmias for desvenlafaxine.
- Cardiac ischemia – there were nine patients that experienced cardiac ischemia events in the desvenlafaxine clinical trials; 6 of the 9 patients had evidence of extensive coronary atherosclerosis. However, because of the known effects of SNRI on blood pressure and heart rate, the Sponsor believes further evaluation is necessary to understand the potential risk.
- Potential suicidality – the Sponsor concluded that there was no pattern suggesting that desvenlafaxine induces suicidality: analyses revealed evenly distributed events across desvenlafaxine, venlafaxine, and placebo treatment groups in the clinical trials. However, because of the concern of a potential association between antidepressants and suicidality, the Sponsor will assess the f _____
- Overdose – the Sponsor recognizes that patients being treated with desvenlafaxine are at increased risk for suicide, via overdose. They believe the clinical trial experience is minimal and that further evaluation is necessary to fully understand the safety profile in overdose conditions.
- Discontinuation effects – The Sponsor believes this event is not expected with desvenlafaxine because of its relatively short half-life of 9-12 hours. However they do not believe they have sufficient information from the clinical trials to determine the effectiveness of a taper in minimizing the risk.
- Hepatic effects – the Sponsor states that there were mild increases in transaminases in the short term trials but no safety signal with regard to adverse hepatic effects. The DPP has conducted a literature review⁹ of hepatotoxicity with venlafaxine and found published case reports of patients who have experienced clinically significant hepatic adverse events. _____
- Effects on serum lipids – the short term trials demonstrated mean increases of approximately 5.8mg/dL, 3.5mg/dL, and 5.2mg/dL in desvenlafaxine patients for total, LDL, and triglyceride levels, respectively, when compared to baseline.

 
The Division of Medication Error and Technical Support (DMETS) has completed a review of the proprietary name, label, and labeling review,¹⁰ and concluded that the proposed proprietary name, Pristiq, is acceptable

⁹ Dubitsky G. Review and evaluation of clinical data: hepatic effects (NDA 20-151 and 20-699); final signature in DFS dated 7/13/06.

¹⁰ Tezky, T. DMETS Proprietary Name, Label, and Labeling Review, OSE Review # 06-0097; dated 10-6-06.

2.3 Drug Use Data

Drug use data was obtained from Verispan, LLC: Vector One[®]: National (VONA) for venlafaxine to ascertain the following information:

- prescriptions by physician specialty
- prescriptions by patient age and gender
- prescriptions dispensed to new patients who have not had a prescription dispensed for an anti-depressant in the past 6 months

Table 1 below shows the total number of prescriptions (new and refills) for venlafaxine dispensed by Retail Pharmacies (Chain, Independent, Food Stores, Mass Merchandisers) in the U.S. (mail order excluded). The data show that the total number of prescriptions for venlafaxine in 2005 is about _____ than 10 years ago. Of note, there has been an important shift in prescribing patterns since 1996. Whereas psychiatrists accounted for _____ the venlafaxine prescriptions written in 1996, they account for _____ of these prescriptions now. Generalists (general and family practitioners, osteopaths, and internists) accounted for approximately _____ of prescriptions in 1996, but account for almost _____ now.

Table 1. Total Venlafaxine Prescriptions by Year and Top 10 Prescriber Specialty* (%)

	Total Rx	PSYCH	GP/FM/DO*	IM	NEURO	OB/GYN	HOSP	NP	RHEUM	PA	PED
1996											
1997											
1998											
1999											
2000											
2001											
2002											
2003											
2004											
2005											
2006											

* GP/FM/DO includes general practice medicine, family medicine, and doctors of osteopathy.
 † = table only includes the top 10 prescriber specialties
 ‡ = year to date, October 2006

_____ Years 1996 – October 2006, Extracted December 2006. Source file: 2006-671 12-1-06 venlafaxine MD.gry

Table 2 below shows the total number of prescriptions for venlafaxine stratified by age for years 2002 to 2006. The data show that the prescriptions for venlafaxine are written primarily for patients aged _____ of age. Use among various age groups has remained relatively stable, although there are trends of _____

Table 2. Venlafaxine Prescriptions Stratified by Age and Year

	2002		2003		2004		2005		2006 ^e	
	Total		Total		Total		Total		Total	
	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share
		%		%		%		%		%
Total Rx										
0-10										
11-20										
21-30										
31-40										
41-50										
51-60										
61-70										
71+										
Unspec.										

^e = year to date, October 2006

Years 2002 – October 2006, Extracted December 2006. Source file: 2006-671 12-1-06 venlafaxine Ag Sx.qry

Dr. Mosholder evaluated the use of venlafaxine as second-line therapy in his review and found that although the use of venlafaxine as second line therapy _____ venlafaxine in comparison to other SSRI antidepressant, approximately _____ of its use was in patients who had not been previously treated with an antidepressant.

2.4 Literature Review of the Impact of Specialized Packaging

Strip packaging or blister packaging coupled with limiting the amount of drug available in preparations has been postulated to reduce the severity of self-poisonings in adults. The OSE recently conducted a review of the literature on the impact of these risk minimization strategies in support of a review of acetaminophen related hepatotoxicity, overdose, and death. The following summary was excerpted from recent review of acetaminophen associated hepatotoxicity.¹¹

In September 1998 the United Kingdom began a program to limit the amount of acetaminophen available over-the-counter; the product became available in blister-packs. Two types of packs were made available – the Supermarket packs contained 16 tablets (500 mg each) and the pharmacy packs contained 32 tablets. A prescription was needed to purchase more than 100 tablets at a time.¹² These changes were made because of concerns that many of the overdoses that occurred were impulsive and blister-packs with limited quantity might decrease the high rate of acetaminophen-related suicides in the UK. An earlier study of 80 patients who chose acetaminophen for overdose reported that 33 (41%) had seriously contemplated taking the overdose for less than one hour

¹¹ Chang YJ, Nourjah P, Ahmad S, Willy M. DRAFT OSE Safety Review: acetaminophen – hepatotoxicity, overdose, and death, RCM # 2006-23.

¹² Turvill JL et al. Change in occurrence of paracetamol overdose in UK after introduction of blister packs. Lancet 2000; 355: 2048-2049.

beforehand and another 26 (33%) for up to 3 hours.¹³ Thirty-three (41%) had obtained the tablets less than an hour before taking the overdose. Forty-three cases (54%) found the tablets in a usual location in the house. The effectiveness of blister-packs as an intervention is difficult to interpret by this study which reported that 60% of his 80 interviewed patients used acetaminophen doses obtained from blister packs (similar to the current sales of blister packs in the UK at the time – 55%) and those patients who took more than 25 tablets, were significantly more likely to use loose pills rather than blister-packs (69% versus 40%); but the investigator also reported that 21 (66%) of those who did not use a blister-pack still would have overdosed on acetaminophen if blister packs were all that was available. A second report by Hawton from the same group of patients found that most did not know that the harmful effects were delayed, with only 18 (22%) realizing the effects would take more than 24 hours.¹⁴

Australian investigators presented their study of the effects of limiting the available tablets of carbamazepine and using strip packaging; this study of a total of 67 patients (51 before and 16 after the 1993 change) showed the number of reported tablets used decreased and the amounts of carbamazepine decreased (although the proportion of patients with coma, the proportion of patients requiring intubation and the time in hospital did not differ significantly).¹⁵ An analysis by Gunnell et al looked at the worldwide availability of acetaminophen by analyzing questionnaires from 12 poisons centers and 5 psychiatrists and by completing a literature review from 23 countries.¹⁶ Gunnell concludes that acetaminophen-related mortality is higher in countries without restrictions, although he acknowledges that his conclusions are based on limited data and not completely consistent, for example, he notes that Sweden had limited access to acetaminophen and relatively high mortality rates. Gunnell suggests that mortality from acetaminophen may be related to a number of different factors, not just access.

As a risk minimization intervention, the introduction of blister packs in the UK is one that has been studied and reported by a number of investigators. The analyses of this strategy have resulted in different findings. Many of the studies from the UK (and other countries) suggest there might be some benefit from restriction of the number of tablets and blister-packs, with a 21% reduction in deaths,¹⁷ 30-50% reduction in severe hepatotoxicity,^{17,18} 31% reduction in admissions,¹⁸ and an 11% reduction in non-fatal overdoses.¹⁷ Other studies did not find a significant reduction in admissions or days of hospital stay,^{19,20} and

¹³ Hawton K et al Paracetamol self-poisoning: Characteristics, Prevention and Harm Reduction. *Br J Psych* 1996; 168:43-48.

¹⁴ Hawton et al Why patient choose paracetamol for self poisoning and their knowledge of its dangers. *BMJ* 1995; 310: 164.

¹⁵ Buckley NA et al. The effect of the introduction of safety packaging for carbamazepine on toxicity in overdose in adults. *Pharmacoepidemiol and Drug Saf* 1995; 4: 351-354.

¹⁶ Gunnell D et al Use of Paracetamol for suicide and nonfatal poisoning: worldwide patterns of use and misuse. *Suicide Life-Threat Behav* 2000; 30: 313-326.

¹⁷ Hawton K et al. Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the UK. *BMJ* 2001; 322:1-7.

¹⁸ Hughes B et al Paracetamol poisoning – impact of pack size restrictions. *J Clin Pharm Ther* 2003; 28: 307-310.

¹⁹ Robinson D et al Severity of overdose after restriction of paracetamol availability. *BMJ* 2000; 321: 926-927.

²⁰ Thomas MR et al Restriction has not reduced admission with self poisoning. *BMJ* 2001; 323:633.

one study reported an increase in overdoses.²¹ The concerns of some that overdoses would switch to other drugs was not supported by some^{22,23} but was supported by others.^{20,24} None of the studies provided overdose information by intention, so it is not clear if any of the reported changes occurred among intentional overdoses or all types of overdoses. Overall, it is difficult to make a summary conclusion given the different study limitations, but there is some suggestion that restriction of the number of tablets and blister-packs may be beneficial.

3 SUMMARY OF PROPOSED RISK MANAGEMENT PLANS

The Sponsor proposes to address the risk of overdose and suicidality in their RMP for both products. The RMP proposal includes product labeling, pharmacovigilance — activities, and risk minimization activities including a medication guide, HCP education, and specialized packaging. —

The Sponsor does not believe that the QT/QRS interval prolongation, adverse hepatic effects, cardiac ischemia, discontinuation effects, and serum lipid effects for desvenlafaxine warrant risk minimization activities beyond product labeling.

3.1 LABELING

3.1.1 Venlafaxine Labeling

The Sponsor submitted a “Changes Being Effective” supplemental application on September 8, 2006 (20-151/SLR-045 and 20-699/SLR-072) that provides for revisions to the Overdose-Human Experience section of the labeling. The labeling supplement was approved on October 20, 2006.

The following language was added at the end of the Overdose-Human Experience section of the label with the approval of the recent labeling supplement:

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristic(s) of venlafaxine-treated patients is not clear. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

²¹ Bateman DN et al Legislation restricting paracetamol sales and patterns of self harm and death from paracetamol-containing preparations in Scotland. *Br J Clin Pharmacol* 2006; 62: 573-581.

²² Turvill JL et al. Change in occurrence of paracetamol overdose in UK after introduction of blister packs. *Lancet* 2000; 355: 2048-2049.

²³ Kisley SR, et al The effect of recalling paracetamol on hospital admissions for poisoning in Western Australia. *Med J Aust* 2003; 178: 72-74.

²⁴ Balit CR et al. Paracetamol recall. *Med J Aust* 2002 ; 176: 162-5.

The following language is included at the end of one paragraph in the Warnings-Clinical Worsening and Suicide Risk section of the label.

Prescriptions for Effexor should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

An initial proposal by DPP in the August 10, 2006 CBE supplemental request letter to add the following language was rejected by the Sponsor because they concluded that “such language may suggest to some practitioners that venlafaxine overdoses at amounts lower than 2,100mg are without risk.”²⁵

Greater than approximately 2,100mg of venlafaxine should not be dispensed at one time to outpatients judged to be at increased risk of suicide (for example, not greater than a 14 day supply at a dose of 150mg/day) (see OVERDOSAGE/Human Experience).

3.1.2 Proposed Desvenlafaxine Labeling²⁶



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3.2 PHARMACOVIGILANCE PLAN

²⁵ Safety Query Response for Venlafaxine: Response to FDA Letter of 10 August 2006 Regarding Venlafaxine Overdose, prepared by Global Safety Surveillance & Epidemiology, Wyeth Research, dated 31 August 2006.

²⁶ NDA 21-992 Annotated Draft Labeling Text, submitted 8 December 2006.

3.2.1 Routine Pharmacovigilance

The Sponsor plans routine postmarketing surveillance via spontaneous adverse event reporting to monitor and evaluate safety signals associated with venlafaxine and desvenlafaxine.

3.2.2 Additional Pharmacovigilance Activities for Desvenlafaxine



3.3 RISKMAP PROPOSAL

The Sponsor has not provided RiskMAP goals but has stated that their objective is to reduce the risk of suicide and fatal overdoses. They plan to do this by communicating safety information in labeling, educating healthcare professional and patients regarding the evaluation and management of patients at times of higher risk for suicidality, and by facilitating the use of a smaller supply during periods of increased risk of suicidality.

3.3.1 Proposed Educational Plan

The main component of the RiskMAP is education. The Sponsor has developed communication and educational activities for venlafaxine to build awareness of updated safety information and associated labeling changes. In addition, educational materials have been developed for clinicians and patients to provide information on the evaluation and management of patients at times of higher risk for suicidal behavior.

The sponsor has conducted two research projects in order to develop their educational plan. The first assessed the administration and use of antidepressants and identified interventions that would help prevent the identified risks. The second analyzed the clinical practice and treatment decisions of physicians with expertise in the management of major depressive disorders. Based on the results of these two projects the Sponsor has developed the components of the educational plan:

- Clinician Resource Program
- Patient Resource Program
- Pharmacists Resource Program
- Small Pack/Unit-of-Use Program

The Sponsor has developed materials and tools to distribute to clinicians and patients and that can be customized to different settings.

The Sponsor has not provided any details of their plan to educate healthcare professionals (HCPs) and patients. They have stated only that they will develop educational materials to support appropriate use with an emphasis on key label safety messages.

3.3.1.1 Target Audience

The target audience has been identified as HCPs and patients.

Comments: This is consistent with the description of risks described in the RMP. However, the characteristics of the targeted HCPs are unclear (e.g., all psychiatrists, all current venlafaxine prescribers?). The sponsor has not described the educational materials to be developed. It is not clear how patients and pharmacists would receive the proposed educational interventions (Patient Resource Program, the Pharmacist Resource Program, and other materials).

3.3.1.2 Education Goals and Objectives

The Sponsor identifies the general goal of the communication and educational activities as building awareness of updated safety information and associated labeling changes for venlafaxine, to provide physicians greater support during treatment of patients with major depressive disorder.²⁷

Comments: This goal seems appropriate to address the identified risks. Specific and measurable objectives that may further describe this goal are not provided (see examples below). These objectives should logically be tied to the four programs listed on page 46 of the RMP and to the educational materials proposed. For example, for the Clinical Resource Program the following objectives could be used:

- *Eighty percent of prescribers will be able to identify the three main methods to evaluate patients at times of higher risks for suicidality.*
- *Seventy-five percent of prescribers will be able to identify the three main methods to manage patients at times of higher risks for suicidality.*

In addition, for the "Patient Resource Program," one objective could be:

- *Ninety percent of patients will be able to recognize at least five early symptoms of depression and what to do whenever those arise.*

3.3.1.3 Educational Materials

The Sponsor issued a "Dear Health Care Provider" letter on October 17, 2006. The purpose of this letter was to inform HCPs about the labeling changes in the recent CBE supplement, to remind HCPs to prescribe the smallest quantity consistent with good patient management, and to inform HCPs about the availability of the smaller unit-of-use packaging.

²⁷ 20-151 and 20-699, Risk Management Plan, dated 11 August 2006, Section 3.4.2, pg 45.

The Sponsor stated that they have developed a core set of customizable educational materials, that would be more likely to be utilized effectively by a wider audience. However, the Sponsor has not submitted these educational materials (for prescribers, patients and pharmacists) to the Agency for review. The Sponsor makes reference to materials to guide and support the treatment practices by physicians, but the relationship of these materials to the four proposed programs (clinician, patient, pharmacy, and small pack) is not clear. We note the DHCP letter mentioned an education and support program entitled "Dialogues: Time-to-Talk," which the Sponsor states is designed to help foster important communication and contact between clinicians and patients. The sponsor has not submitted the educational materials to the Agency for review, but the letter points HCPs to a website (www.mddpatientsupport.com) where a list of materials and links to those materials are available.

Comments:

The appropriateness of the educational activities and materials, in terms of their content and the means to identify risks, cannot be determined until these activities and materials, and their implementation plan, are fully detailed.

The sponsor has collected the information upon which to base the rationale for the four proposed educational programs by engaging in two research projects (RxFMEA, CareMAP).²⁸ These projects represent the collection of critical information for the appropriate development of educational interventions. As part of these projects, behaviors related to the treatment of patients, activities, language, and procedures that clinicians use in the care of patients with major depressive disorder (MDD) have been identified by the Sponsor; however, they are neither listed nor described in the RMP. Furthermore, barriers to the treatment of MDD have been identified but not described. Details of the major findings of these projects, which led to the development of the educational materials, are critical for the review of the educational interventions. However, the sponsor did not submit these with the RMP.

3.3.2 Modification of Packaging

The Sponsor is introducing a small pack/unit-of-use to facilitate the dispensing of a smaller supply (approximately 2 weeks) of venlafaxine and desvenlafaxine. The RMP proposal states that the modified packaging should be used during periods of increased risk of overdose, and defines these periods as dose initiation, titration, or change. They state that this measure will reduce the amount of venlafaxine available and limit the toxicity should a patient take it in overdose.

Comments:

Modified packaging appears on its face to be a pragmatic approach to reducing overdose toxicity; and this approach coupled with blister packs have had positive findings with regard to reducing overdoses in some countries. However, OSE has concerns regarding the practicality of the modified packaging.

²⁸ 20-151 and 20-699, Risk Management Plan, dated 11 August 2006, Section 3.4.2, pg 46.

strategy is similar for desvenlafaxine; however, details of the Sponsor's educational plan were not detailed in their RMP submission.

We have concerns that this risk management strategy may not go far enough in reducing the overdose risks. Although there is some evidence that smaller packs coupled with blister packing has had an effect of reducing suicides in other countries, we are not convinced that this strategy will succeed in the U.S. The proposed voluntary smaller pack is not supported by labeling, and does not fit with usual medication insurance practices. Such packaging may not be adopted by generic companies. Moreover, use of the smaller pack would only have a potential impact on patients who impulsively commit suicide. Patients who plan suicide would be able to stockpile drug, irrespective of whether smaller packs are implemented.

The Division may need to consider additional approaches to minimizing this risk, including the consideration that venlafaxine and desvenlafaxine be reserved as second-line therapy. Verispan data indicate that the use of venlafaxine has increased overall in the past 10 years, and the proportion of prescriptions by non-psychiatrists has increased considerably. Use data also indicate that venlafaxine is being used as a first line antidepressant drug in up to 1/3 of prescriptions written. In order to minimize the risk of overdose toxicity as well as the potential cardiovascular consequences of sustained hypertension with these products, the Division and Sponsor should consider ways to minimize exposure including limiting the MDD indication for venlafaxine and desvenlafaxine to patients who have not benefited from less toxic antidepressants.

If the Division is not prepared at this time to take this approach, we recommend that the Sponsor comprehensively evaluate the risk management strategies described in their submissions on overdose toxicity and suicide. In addition, they should provide more details on their risk management strategies, particularly how they plan to implement the smaller pack. As the risk profiles for desvenlafaxine and venlafaxine are similar, the risk management strategies, including labeling, should be the same as well.

4.1 Comments for Sponsor (apply to desvenlafaxine and venlafaxine)

Regarding RiskMAP Evaluation Activities

- Provide a plan of how you plan to evaluate the impact of the modified packaging and other risk management strategies on overdose toxicity and suicide
- Submit a full protocol that includes a more detailed description of your survey methodology, that includes (but is not limited to):
 - The numbers of patients and prescribers who will be surveyed
 - An explanation of methods to be used to determine the sample
 - A clear definition of the selection criteria
 - An explanation of the controls to be used to minimize bias
 - An explanation of the controls to be used to compensate for the limitations associated with their methodology
 - Submission of the survey instrument (questionnaire and moderator's guide).

Regarding the Modified Packaging Plan

- Provide details on how this packaging has been implemented for venlafaxine and how it will be implemented for desvenlafaxine, including:
 - Whose responsibility it is for ensuring that high risk patients are dispensed only the small pack
 - What the pharmacists' role is to be in dispensing the small pack, and how they are to be informed about its purpose
 - How the proposed packaging configuration is different than a physician writing a prescription for a small quantity, especially since the proposed packaging does not convey any messages to the pharmacist.

Regarding the Proposed Education Plan:

- The focus of the educational plan should be to educate HCPs, not only in identifying high risk patients, but also in when and how to write prescriptions appropriately for high risk patients.
- The HCP target population for your education and outreach should be all psychiatrists and other physicians and healthcare providers who are currently prescribing venlafaxine.
- The education plan should also target pharmacists specifically with regard to the importance and purpose of the 15-day unit-of-use pack.
- Provide clear and measurable objectives for the Clinician Resource Program, the Patient Resource Program, the Pharmacists Resource Program, and the Small Pack/Unit-of-Use Program. For example, for the Clinical Resource Program, the following objectives could be used:
 - Eighty percent of prescribers will be able to identify the three main methods to evaluate patients at times of higher risks for suicidality.
 - Seventy-five percent of prescribers will be able to identify the three main methods to manage patients at times of higher risks for suicidality.In addition, for the "Patient Resource Program," one objective could be:
 - Ninety percent of patients will be able to recognize at least five early symptoms of depression and what to do whenever those arise.
- Identify and describe the barriers to the treatment of major depressive disorder that these four programs intend to address.
- Describe the major findings of the RxFMEA project and the CareMAP project, and describe how these findings led to the development of the four programs proposed and listed on page 46 of your submission.
- Provide a description of the Clinician Resource Program, the Patient Resource Program, the Pharmacists Resource Program, and the Small Pack/Unit-of-Use Program, including a description of their plan for implementation.
- Provide a description of the "practical materials and tools, developed to distribute to clinicians and patients," and describe the implementation plan for these materials, in particular, how these will be used by the clinicians and patients.

Additional Comments

- The Sponsor should report to the Agency the status of any efforts and data relating to their risk management plan. Information should include but not be limited to:
 - Complete venlafaxine use data including extent of use as a first or second line agent, as well as the extent to which the small pack is being prescribed/dispensed. This information should be provided during the reporting period, as well as cumulatively.
 - Results of the physician and patient survey analysis
- For venlafaxine this information should be submitted six months after the RMP has been implemented and yearly thereafter. The yearly submission could be included in the Sponsor's Periodic Report.
- For desvenlafaxine, this information should be submitted every six months for the first three years and could be included in every other Quarterly Periodic report submitted to the Agency, beginning with the second Quarterly report.

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