Addendum to Clinical Review
sNDA #21992/S-042

Sponsor:	Pfizer
Drug:	Desvenlafaxine Extended Release Tablets
Proposed Indication:	Major depressive disorder (MDD)
Material Submitted:	sNDA #21992/S-042
Correspondence Date:	April 6, 2017
Date Received:	April 6, 2017
Serial Number:	1116
DARRTS SDN:	0330

Background

Pristiq (desvenlafaxine) is a serotonin and norepinephrine reuptake inhibitor (SNRI) that was approved for major depressive disorder in 2008. Desvenlafaxine is the active metabolite of venlafaxine, which was approved in 1997. The exact mechanism of desvenlafaxine/venlafaxine is unknown, but may be related to an induction of increased serotonin and norepinephrine activity in the central nervous system, through inhibition of their reuptake. The Pristiq approval carried a Postmarketing Commitment (PMC #1229-1) under the Pediatric Research Equity Act (PREA) to conduct two studies to assess the safety and efficacy of Desvenlafaxine Extended Release Tablets (DVS SR) in the treatment of children and adolescents (ages 7 to 17 years) with MDD. These studies were performed under IND 64552 and were submitted in this supplement.

In addition, this supplement also required revision of Pristiq labeling to conform to the Pregnancy and Lactation Labeling Rule (PLLR). The Division of Psychiatric Products consulted the Division of Pediatric and Maternal Health (DPMH) for recommendations regarding changes to the label in Sections 8.1, 8.2, and 8.3. The results of their consultation were pending as of December 29, 2017, when the medical officer's clinical review of the PREA studies contained in the application was completed. Significant labeling issues are described here as an addendum to the medical officer's clinical review.

II. Review of Significant Clinical Labeling Issues

Labeling reviews for this supplement included:

- DPMH Maternal Health Team PLLR Labeling Review completed by Leyla Sahin, MD on January 8, 2018. Dr. Sahin reviewed data in this supplement as well as data from her own literature review to recommend language pertaining to human

pregnancy risk in Section 8.1, lactation in Section 8.2, effects on reproductive potential in Section 8.3, and patient counseling information regarding pregnancy in Section 17. Dr. Sahin considered the following issues: major birth defects, hypertensive disorders of pregnancy, postpartum hemorrhage, spontaneous abortion, persistent pulmonary hypertension of the newborn, neonatal withdrawal, information from a published lactation study, and fertility effects in humans. Dr. Sahin took the lead in crafting text for the above sections of draft labeling.

Dr. Sahin's review noted that there are no published data on desvenlafaxine exposure in pregnancy, so available data from published literature on venlafaxine exposure during pregnancy was reviewed to guide labeling. An increase in blood pressure in the nonpregnant population is a labeled adverse reaction with Pristiq; therefore, it is biologically plausible that an increase in blood pressure may occur during pregnancy. Additionally, increased blood pressure is a known risk factor for preeclampsia. Based on available epidemiologic data that have consistently shown an association between venlafaxine use in pregnancy and preeclampsia, it is reasonable to include a clinical considerations statement in labeling that desvenlafaxine use in pregnancy may be associated with an increased risk of preeclampsia, and to include a summary of the data under the Human Data heading. Available data from published literature on venlafaxine exposure in pregnancy have shown an association with postpartum hemorrhage. Abnormal bleeding in the nonpregnant population is a labeled adverse reaction in Pristiq labeling; therefore, it is biologically plausible that postpartum hemorrhage may occur. It is appropriate to include a clinical considerations statement in labeling that desvenlafaxine use late in pregnancy may be associated with postpartum hemorrhage and to include a summary of the data under the Human Data heading. Available data from published literature on venlafaxine during pregnancy have not reported a clear association with venlafaxine and adverse developmental outcomes. Available data from published literature on venlafaxine during pregnancy and spontaneous abortion are based on two small studies that have shown conflicting results; therefore, it is reasonable to not include this information in labeling. Unlike SSRIs, available published studies did not associate serotonin and norepinephrine reuptake inhibitors (SNRIs) as a class with persistent pulmonary hypertension of the newborn (PPHN). However, the data are not sufficiently robust to conclude that PPHN is not associated with use of venlafaxine/desvenlafaxine.

- Office of Prescription Drug Promotion (OPDP) Pre-Decisional Agency Information Memorandum completed by Aline Mouktara, Acting Team Leader in OPDP, on January 5, 2018. This memorandum commented on numerous sections of the entire labeling.

- Patient Labeling Review completed by Shawna Hutchins, of the Division of Medical Policy Programs (DMPP), and Christine Bradshaw, PharmD, of OPDP,

on December 18, 2017. This review recommended several revisions to the Pristiq Medication Guide.

Recommendations for labeling changes conveyed in the above reviews were discussed at labeling meetings for this supplement and, as appropriate, incorporated into labeling after negotiations with the Applicant. Overall, major revisions to labeling included the following:

- Relocation of the description of important pediatric safety data from Section 6.3 to Section 8.4.
- Conversion of Sections 8.1 through 8.3 to PLLR format.
- Addition of pediatric pharmacokinetic data and a description of the juvenile animal studies to Section 8.4.
- Deletion of Section 14.2 which summarized efficacy results from the two negative pediatric efficacy trials in MDD.
- In Section 8.1, a discussion of the risk of discontinuing antidepressant medication during pregnancy as well as the risk of SNRI associated preeclampsia and postpartum hemorrhage.
- In Section 8.1, a discussion of the background risk of major birth defects and miscarriage and the limitations of existing studies which have examined these risks in pregnant women exposed to venlafaxine.

III. Conclusions and Recommendations

Women diagnosed with MDD who discontinue their antidepressant medication before or during pregnancy are at a greater risk of relapse than those who continue their medication. Also, a mood disorder such as MDD or bipolar disorder existing prior to pregnancy is a risk factor for postpartum depression. Depression during pregnancy has been associated with poor obstetrical and neonatal outcomes. Based on the above considerations from the available data, the changes to the label convey a reasonable description of the risks and benefits of desvenlafaxine exposure in pregnancy.

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/s/

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02/27/2018

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