CLINICAL REVIEW

Application Type	sNDA
Application Number	21992/S-042
Priority or Standard	Standard
Submit Date(s)	April 6, 2017
Received Date(s)	April 6, 2017
PDUFA Goal Date	February 6, 2018
Division / Office	DPP/ODE1
Reviewer Name(s)	John C. Umhau MD MPH
Review Completion Date	December 29, 2017
Established Name	Desvenlafaxine Extended Release Tablets
Trade Name	Pristiq
Therapeutic Class	Serotonin and norepinephrine reuptake inhibitor (SNRI)
Applicant	Pfizer
Formulation(s)	50 mg and 100 mg tablets
Dosing Regimen	Once daily
Indication(s)	Major depressive disorder
Intended Population(s)	7 to 17 years

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Desvenlafaxine succinate sustained release (DVS SR) tablets failed to show efficacy over placebo in pediatric patients ages 7-17 with major depressive disorder (MDD) in two short-term pivotal trials. There were no significant new safety signals observed in the MDD pediatric studies. Therefore, I recommend approval of this supplement with revisions to Section 8.4 of Pristiq labeling to reflect the safety and efficacy data from these studies.

1.2 Risk Benefit Assessment

Based on the failure of DVS SR to show efficacy in pediatric patients with MDD, the risk of use outweighs the benefit in this population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None. Pristiq is not currently subject to a REMS and there were no safety findings from the reviewed studies that would warrant a REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

None. The Applicant's request for a waiver of additional studies for the maintenance treatment of MDD (PMR #2053-1) in ages 7-17 years is reasonable considering that DVS SR failed to demonstrate a meaningful therapeutic benefit over placebo in two short-term trials.

2 Introduction and Regulatory Background

2.1 Product Information

DVS SR (brand name: Pristiq) is an antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI) class developed and marketed by Wyeth (now part of Pfizer). It is the active metabolite of venlafaxine, an SNRI which was first approved in the U.S. in 1993 and is marketed as Effexor and Effexor XR.

2.2 Currently Approved Treatments for Major Depressive Disorder in Pediatric Patients

Approved treatments for MDD in pediatric patients are noted in the table below:

Table 1 Currently Approved Treatments for Major Depressive Disorder in Pediatric Patients

SSRI
Escitalopram (ages 12 to 17 years)
Fluoxetine (ages 8 to 17 years)

Source: Self compiled.

2.3 Availability of Proposed Active Ingredient in the United States

DVS SR was approved in the U.S. in 2008 and is marketed in the United States as Pristiq.

2.4 Important Safety Issues with Consideration to Related Drugs

Suicidal ideation and behavior have been concerns with antidepressant drug treatment of patients under 25 years of age. Venlafaxine may adversely affect weight and height in children, and in pediatric patients (ages 6-17), blood pressure and cholesterol increases were observed in a fashion that was similar to that observed in adult patients. Other potential safety issues with DVS SR are:

- Hypersensitivity reactions, including angioedema.
- Serotonin syndrome, particularly with the concomitant use of other serotonergic drugs such as MAOIs.
- Abnormal bleeding, especially with the use of NSAIDs, aspirin, and other drugs that affect coagulation or bleeding.
- Angle closure glaucoma.
- Activation of mania or hypomania.
- Discontinuation syndrome, which is more frequent with longer treatment duration.
- Seizures.
- Hyponatremia.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

DVS SR was approved on February 29, 2008, for the treatment of adult patients with MDD under NDA 21992 as Pristiq Extended-Release Tablets. The original Applicant, Wyeth, agreed to conduct two studies under PREA to assess the safety and effectiveness of DVS SR as a treatment for MDD in children and adolescents. According to PMC 1229-1, children (ages 7 to 11 years) and adolescents (ages 12 to 17 years) were to be equally distributed and there was to be a reasonable distribution of sexes in these age groups. Wyeth agreed to submit the results the results no later than 4.5 years after the approval date for Pristiq. Also, a Pediatric Written Request (PWR)

including these two trials was issued on February 10, 2009, and was amended on March 22, 2010. Study reports were to be submitted to the Agency on or before March 2014. On December 1, 2012, all rights to the NDA were transferred from Wyeth to Pfizer, who submits the data in this sNDA to fulfill PREA requirements. There have been numerous interactions between the Applicant and the FDA concerning this program, which was most recently discussed at a Type B (telecon) meeting on May 25, 2016. Topics included safety issues in children observed with the related drug, Effexor XR, including an effect on weight and height particularly if treatment is long-term. In the Effexor XR studies conducted in pediatric patients (ages 6-17), the occurrence of blood pressure and cholesterol increases considered to be clinically relevant in pediatric patients was similar to that observed in adult patients. There was also some concern of an increase in suicide and aggressiveness.

This submission is intended to fulfill the PREA requirement to conduct two studies in the pediatric patients (ages 7 to 17 years inclusive) with MDD.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of the submission was adequate for a complete and thorough review. For three patients, I reviewed narrative summaries and case report forms for adverse events and traced the data to show that it appeared in the datasets of adverse events associated with the particular study. No issues with the integrity of the data were noted.

3.2 Compliance with Good Clinical Practices

All 6 studies were conducted following Good Clinical Practices (GCP).

Protocol B2061032 Site 1054 was closed at the sponsor's initiative due to unconfirmed but serious allegations of GCP misconduct and concerns about data integrity. This site's data were included in the primary analysis which is consistent with correspondence received from the FDA recommending that the primary analysis include all data from all sites. Given the FDA feedback and the site's limited enrollment (5 subjects randomized representing 1.4% of the ITT population), the sponsor decided not to conduct a sensitivity analysis to exclude this site's data from the primary efficacy analysis.

3.3 Financial Disclosures

Clinical Investigator Financial Disclosure Review Template

Application Number: NDA 21992/S-042

Submission Date(s): April 6, 2017

Applicant: Pfizer

Product: Pristiq

Reviewer: John Umhau MD MPH

Date of Review: October 17, 2017

Covered Clinical Study (Name and/or Number): B2061031, B2061032, B2061030, 3151A62001, 3151A62000, B2061014

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 972		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 8		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The applicant has provided adequate disclosure of financial relationships and arrangements which may have compromised the integrity of the research.

One investigator who participated in Study B2061014 (Site (b) (6)) as well as in the open-label extension Study B2061031 had disclosable financial information. Dr. (b) (6) received a sum greater than $24,999.00 from the Applicant as speaking fees and honoraria. Site (b) (6) randomized a total of (b) (6) patients of 340 randomized in the study as a whole.

One subinvestigator in Study B2061014 (Dr. (b) (6) at Site (b) (6)) was a part-time or full-time employee of the Applicant. Dr. (b) (6) was also an investigator in the open-label extension Study B2061031. A total of (b) (6) patients were randomized at this site out of 340 randomized in the entire study.

A total of (b) (6) patients were randomized at these two sites, which is less than 5% of the total number of randomized patients in Study B2061014. The fact that patients were randomized to double-blind treatment in this trial mitigates against bias in the study conduct on the part of these two investigators.

Eight of the 972 investigators involved in the studies did not provide financial disclosure and information could not be obtained following due diligence by the Applicant. The potential of such a relatively few missing disclosure forms to compromise the data integrity seems minimal.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new information was contained in this supplement.

4.2 Clinical Microbiology

No new information was contained in this supplement.

4.3 Preclinical Pharmacology/Toxicology

No new information relevant to this PMC was contained in this supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

No new information was contained in this supplement.

4.4.2 Pharmacodynamics

A pharmacodynamic analysis included 411 subjects (including 97 in placebo group) who had both baseline and Week 8 measurements of the Childhood Depression Rating Scale-Revised (CDRS-R) in the two short-term Phase 3 studies. PD effects were described using a linear function relating DVS AUC from the last dose of DVS SR to the change from baseline in CDRS-R at Week 8 (CDRS-R). However, the slope of this linear function was not significantly different from 0, suggesting no relationship between DVS AUC and change in the CDRS-R.

4.4.3 Pharmacokinetics

A pharmacokinetic (PK) study in children and adolescents (Study B2061012) treated with fixed doses of DVS SR showed the following:

- Linear increases in Cmax and AUC with increasing doses in children and adolescents.
- Oral clearance was higher in children than adolescents but with considerable overlap in values due to variability.
- Clearance in adolescents was similar to that observed in adults.
- Urinary elimination of desvenlafaxine over 72 hours was similar in children, adolescents, and adults.
- AUC values were reasonably predicted based solely on body weight.

A population pharmacokinetic (PPK) database included 342 evaluable subjects with 1165 PK records. The PPK database had data from subjects ranging in age from 7 to 17 years (mean age: 12.8 years). Weights ranged from 20 to 145 kg. Among the evaluable 342 subjects, there were 145 males and 197 females.

Weight was found to be predictive for apparent oral dose clearance (dose/AUC) and weight and age were found to be predictive of volume of distribution.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The pediatric program is comprised of six studies (see Table 2):

- A PK study and its open label extension study (B2061012 and B2061013, respectively).
- Two double blind, randomized Phase 3 studies (B2061014 and B2061032) and their associated open-label extension studies (B2061031 and B2061030, respectively).

Table 2 Clinical Studies (Pristiq Pediatric Program)

Study No	Phase	Treated (N)	Type of Study	Total Daily Dose	On-therapy
B2061012	2a	59	OL, PK, Short-term	DVS SR CHD (10, 25, 50, 100 mg) ADL (25, 50, 100, 200 mg)	8 weeks
B2061013	2a	40	OL, EXT to 1012	DVS SR Flex dose CHD (10-100 mg/day); ADL (25-200 mg/ day)	26 weeks
B2061014	3	339	DB, PC, Randomized, Short-term	DVS SR High Dose Exposure[a], Fluoxetine 20 mg, Placebo	8 weeks
B2061031	3	268	OL, EXT to 1014	DVS SR Flex dose: 20 mg, 25 mg, 35 mg, and 50 mg	26 weeks
B2061032	3	363	DB, PC, Randomized, Short-term	DVS SR High Dose Exposure, DVS SR Low Dose Exposure Placebo	8 weeks
B2061030	3	281	OL, EXT to 1032	DVS SR Flex dose: 20 mg, 25 mg, 35 mg, and 50 mg	26 weeks

ADL = Adolescent; CHD = Children; DB = Double-Blind; DVS = Desvenlafaxine Succinate; Flex dose = Flexible dose; SR=Sustained Release; N = Number of Subjects; OL = Open Label; PC = Placebo-Controlled; PK = Pharmacokinetic, EXT = extension. DVS SR High / Low Dose Exposure: Subjects were assigned a DVS SR dose based on their weight at baseline as in Table 3 below.

5.2 Review Strategy

The overall clinical review strategy consisted of the following:

- examination of the efficacy results from each of the two key efficacy trials (B2061014 and B2061032).
- evaluation of deaths, serious adverse events, adverse events that led to dropouts, and other significant adverse events among DVS SR-treated patients across all six studies in the pediatric program.
- review of common adverse events and changes in laboratory, vital sign, ECG, and suicidality measures in the pool of the short-term, placebo-controlled Phase 3 studies (B2061014 and B2061032).

5.3 Discussion of Individual Studies/Clinical Trials

Study B2061014 was a multicenter, randomized, double-blind, placebo-controlled, fluoxetine-referenced, parallel-group study to evaluate the efficacy, safety and tolerability of DVS SR in children and adolescent outpatients with MDD.

Study B2061032 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety and tolerability of a high and a low dose of DVS SR in children and adolescent outpatients with MDD.

These two trials were reviewed individually to evaluate the efficacy of DVS in treating children and adolescents with MDD. The study designs and results are presented in Section 6. There were no major safety findings noted in the data derived from these studies.

6 Review of Efficacy

Summary

The two Phase 3 placebo-controlled studies did not demonstrate efficacy at Week 8 on the primary endpoint, the Children's Depression Rating Scale-Revised (CDRS-R), and therefore cannot support an efficacy claim in for use in pediatric MDD patients.

6.1 Indication: Major Depressive Disorder

6.1.1 Methods

Objectives

Pivotal Studies B2061014 and B2061032 were designed to evaluate the efficacy of DVS SR compared with placebo in the treatment of children and adolescents with MDD in addition to assessing safety and PK.

Study Design

Studies B2061014 and B2061032 included a screening phase, a double-blind treatment phase for 8 weeks, a 1-week double-blind taper/transition phase, and a 4-week follow-up phase. Study B2061014 compared a high dose DVS to placebo in a study using fluoxetine 20 mg/day as an active control. Study B2061032 compared both a DVS SR high dose exposure and DVS SR low dose exposure to placebo. DVS dosing was based on body weight and was determined as shown in the table below.

Table 3 DVS Target Doses Based on Body Weight

Baseline Weight	Low Dose Arm	High Dose Arm
≥20 and <35 kg	20 mg	25 mg
≥35 and <70 kg	25 mg	35 mg
≥70 kg	35 mg	50 mg

Design features common to both B2061014 and B2061032 included:

- Lower starting dose with a step up to the target dose after one week.
- Step down to the lower dose for one week after completion of the 8-week treatment phase.
- Enrollment of enough subjects per treatment arm in order to have 85% power to detect a difference of at least 5 units (CDRS-R score points) between DVS SR and placebo at a level of significance of 5%.
- Interim analysis to assess the standard deviation of the primary efficacy endpoint for potential sample size adjustment.

Patient Selection

Inclusion and Exclusion Criteria

The subjects enrolled in Study B2061014 and B2061032 were male or female outpatients, aged 7 to <18 years and ≥20 kg in weight, and in generally good health. Key inclusion criteria required that all subjects were to have a diagnosis of MDD, as assessed by the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) and clinical interview, with CDRS-R score >40 and Clinical Global Impression of Severity (CGI-S) score ≥4. Subjects were to have a current DSM-IV-TR Major Depressive Episode of at least moderate severity for at least 1 month before screening.

Exclusion criteria included: presence of a serious medical condition; suicidal ideation with some intent to act or specific plan and intent to act, or lifetime history of suicide behaviors; blood pressure elevations; history of electroconvulsive therapy; history of anorexia or bulimia; history or presence of any psychotic disorder; current psychoactive substance or alcohol abuse or dependence; current anxiety disorder or attention deficit hyperactivity disorder if considered to be the primary diagnosis or causing more stress or impairment than MDD; clinically important personality disorder; history of failure to

respond to an adequate course of treatment for MDD with fluoxetine, venlafaxine, or desvenlafaxine.

Assessments

In each study, the primary efficacy endpoint was the change from baseline of the CDRS-R total score at Week 8. The key secondary endpoint was the change from baseline of the CGI-S score at Week 8. These measures were obtained at Weeks 1, 2, 3, 4, 6, 8, 9 and/or the Early Termination study visits as appropriate.

Analysis Plan

The primary null hypothesis for both studies was that there was no difference between DVS SR treatment and placebo with respect to the mean change from baseline in CDRS-R total score at Week 8.

For Both Study B2061032 and B2061014, the primary analysis was conducted on the change from baseline in the CDRS-R total score at Week 8 (primary time point) based on the ITT population. A mixed-effects model for repeated measures (MMRM) was used with treatment, week, interaction of treatment and week, age group, and gender as fixed effects and the baseline CDRS-R total score as a covariate. Data from visits on therapy were used.

For Study B2061032, a Hochberg step-up procedure was used to control for multiplicity associated with multiple active dose exposure groups. If both DVS SR exposure groups had p-values ≤0.05, they were both declared statistically significant; if one DVS SR exposure group had a p-value >0.05 and the other DVS SR exposure group had a p-value ≤0.025, this other DVS SR exposure group alone was declared statistically significant. The time profile based on the MMRM analysis was also presented.

For Study B2061014, If the p-value associated with the comparison was less than 0.05, then DVS SR would be declared statistically superior to placebo with respect to the primary efficacy endpoint. The time profile based on the MMRM analysis was also presented. The comparison of fluoxetine to placebo was conducted for assay sensitivity purposes only.

For both Study B2061032 and B2061014, last observation carried forward (LOCF) and observed cases (OC) approaches were used as sensitivity analyses on the change from baseline in the CDRS-R total score at each post-baseline visit. These analyses utilized an analysis of covariance (ANCOVA) model with treatment, age group, and gender as fixed effects and the baseline CDRS-R total score as a covariate.

6.1.2 Demographics

Table 4 Demographics (All Six Pediatric Studies – DVS SR Patients Only)

Age Group	Males	Females	Total
7 to 11 years	140	106	246
12 to 17 years	178	260	438

Table 5 Demographics (Study B2061014 – All Patients)

Age Group	Males	Females	Total
7 to 11 years	73	57	130
12 to 17 years	82	127	209

Table 6 Demographics (Study B2061032 – All Patients)

Age Group	Males	Females	Total
7 to 11 years	63	46	109
12 to 17 years	95	159	254

6.1.3 Subject Disposition

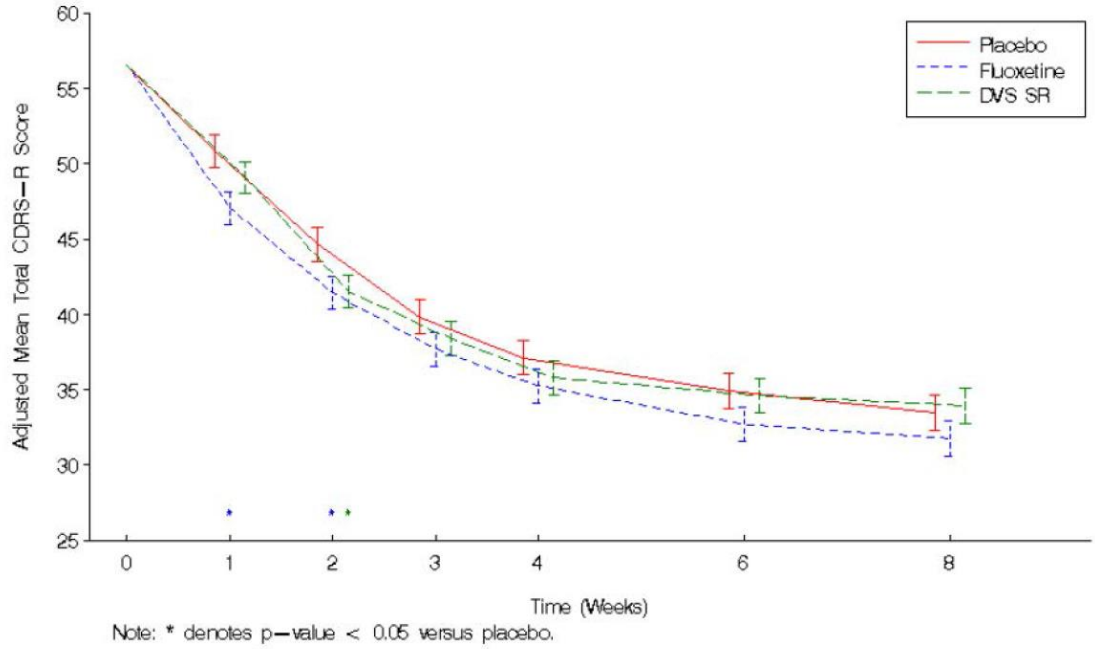
In study B2061014, 340 subjects were randomized, and 85% completed. In study B2061032, 363 subjects were randomized, of whom 83% completed the study. The occurrence of an adverse reaction was the most common reason for subjects to drop out of the study. Five percent withdrew from the study due to an adverse event in study B2061032 as well as in study B2061014.

6.1.4 Analysis of Primary Endpoint(s)

The statistical reviewer concluded that although efficacy was not demonstrated in any of the treatment groups, both studies were adequately powered to detect a targeted treatment difference, which we agreed upon.

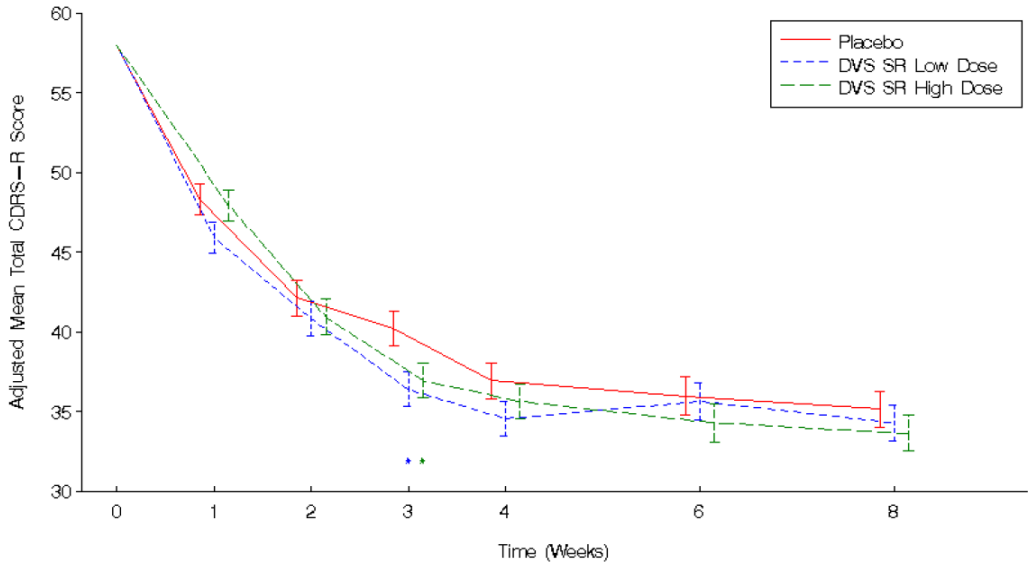
In study B2061014, placebo, fluoxetine, and DVS SR-treated groups all showed improved CDRS-R scores, but there were no group differences. The improvement was essentially identical in DVS SR-treated subjects compared to placebo subjects.

Figure 1 CDRS-R Total Score Over Time (Study B2061014)



In study B2061032, there was no group difference on the primary endpoint, the Week 8 adjusted change in CDRS-R total score. The results were -23 in the low dose group compared to -23 in the placebo group, a non-significant difference (p= 0.85). Only at one time point, week 3, was there a significant improvement over placebo, p=0.013 for the low dose and p=0.034 for the high dose. The adjusted change from baseline in CDRS-R total score at Week 8 was -24 in the DVS SR high dose exposure group, as compared to -23 in placebo-treated subjects, a non-statistically significant treatment difference of 1.5 (95% CI -1.6, 4.6), p=0.33.

Figure 2 CDRS-R Total Score Over Time (Study B2061032)



In sum, there were two Phase 3 placebo-controlled studies conducted to determine the effect of DVS SR on children with MDD. Study B2061014 failed because neither it nor the positive comparator, fluoxetine, showed a significant effect on the on the primary endpoint, change in the CDRS-R total score at week 8. Study B2061032 was negative; it also did not show an effect of DVS SR on this same primary endpoint.

6.1.5 Analysis of Secondary Endpoints(s)

For both studies B2061014 and B2061032, the statistical analysis plan (SAP) established that the significance of the key secondary endpoint, the CGI-S, would be conditional to the results for the primary endpoint. Since statistical significance was not observed for the primary endpoint in either study, the results of the CGI-S could not be deemed to establish efficacy in either study.

For study B2061014, the nominal p-value observed for the comparison between DVS SR and placebo-treated subjects at Week 8 was p=0.94 and the nominal p-value for the comparison between fluoxetine and placebo was p=0.22.

For Study B2061032, the nominal p-value observed for the comparison between the DVS SR low dose group and placebo-treated subjects at Week 8 was p=0.92 and the nominal p-value for the comparison between the DVS SR high dose group and placebo-treated subjects was p=0.30.

6.1.6 Other Endpoints

For Study B2061014, no statistically significant differences were observed at any time point between the actively treated subjects versus placebo in regards to the distribution of CGI-I scores (p >0.05). Response on the CGI-I was defined as a score of 1 (very much improved) or 2 (much improved). At Week 8, the percentage of subjects who were scored as very much improved was 23% in the DVS SR arm compared to 31% in the fluoxetine arm and 27% in placebo. At Week 8, the percentage of patients with scores for much improved was 46% in the DVS arm compared to 48% in the fluoxetine arm and 36% in placebo. At Week 8, the percentage of all responders was statistically significantly higher (p=0.02) in the fluoxetine-treated subjects (78%) compared to the placebo treated subjects (63%).

For Study B2061032, no statistically significant differences (p ≤0.05) were observed between the actively treated subjects versus those treated with placebo in regards to the distribution of CGI-I scores at all time points. At Week 8, the percentage of subjects with scores of very much improved was 19% in the DVS SR low dose group and 26% in the DVS SR high dose group compared to 22% in the placebo group. At Week 8, the percentage of subjects with scores for much improved was 37% in the DVS SR low dose group and 37% in the DVS SR high dose group compared to 34% in the placebo group. At Week 8, the percentage of all responders was not statistically significantly different (p=0.93) in the DVS SR low dose group (56%) compared to the placebo-treated subjects (56%) or in the DVS SR high dose group (62%) compared to the placebo-treated subjects (56%).

6.1.7 Subpopulations

For the analysis of subpopulations, the populations of the two efficacy studies were pooled. In the pooled analysis, the effect of the interactions between treatment and each of the factors was not found to be statistically significant at most time-points. At Week 8, no statistically significant differences were found between the treatment effect of the subgroups (children versus adolescents, males versus females, and Black versus White or other races versus White). In general, the results of the analysis by subgroups were consistent with those found for the analysis of all subjects, i.e. at Week 8 no statistically significant differences were observed between the DVS SR-treated arms and placebo (apart from DVS SR high dose in female children (p=0.047)), and statistically significant differences at isolated time-points).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The population pharmacokinetics (PPK) and pharmacokinetic-pharmacodynamic (PK-PD) analysis to explore the relationship between DVS SR exposure area under the curve (AUC) and the key efficacy endpoint (the change from baseline in CDRS-R total

score at Week 8), did not suggest a relationship between DVS AUC and the key efficacy endpoint at the doses studied in Phase 3 studies B2061014 and B2061032.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not analyzed.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

There were no new safety signals identified in the pediatric program.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The pediatric program is comprised of six studies:

- A PK study and its open label extension study (B2061012 and B2061013, respectively).
- Two 8-week, double blind, randomized Phase 3 studies (B2061014 and B2061032) and their associated open-label, flexible-dose extension studies (B2061031 and B2061030, respectively).
    - B2061014 compared high-dose DVS SR and fluoxetine 20 mg to placebo.
    - B2061032 compared high-dose and low-dose DVS SR to placebo.

7.1.2 Categorization of Adverse Events

Adverse event verbatim terms were coded to preferred terms using MedDRA. Although an audit of the coding process revealed no major errors, the granularity of MedDRA does permit splitting of some adverse events to an extent that may not be clinically useful. Therefore, for purposes of this review, numerous related adverse event preferred terms were combined into a common term for calculation of reporting rates. See Section 9.4 for a listing of adverse events terms that were combined into common terms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data were analyzed in two pools: Set A was considered the primary safety database and consisted of data from the two short-term Phase 3 double-blind, placebo-controlled studies (B2061014 and B2061032) and Set B consisted of data from DVS SR exposed patients from all six pediatric studies.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

There was a total of 684 subjects exposed to DVS SR in the pediatric program; 376 were exposed for <6 months, and 308 were exposed for ≥6 months. Male and female children and adolescent were enrolled in numbers that are expected for the pediatric MDD population (see Table 7 below).

Table 7 Male and Female Children and Adolescents Exposed in the Pediatric MDD Program

Age Group	Males	Females	Total
7 to 11 years	140	106	246
12 to 17 years	178	260	438

7.2.2 Explorations for Dose Response

Study B2061032 utilized two fixed dose levels. There was no evidence that increased dose produced an increased response on the CDRS-R and there was no relationship between DVS AUC and change in the CDRS-R total score.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Safety data including adverse events, vital signs, EKG's, physical exams, and laboratory evaluations from these studies were reviewed in Set A and B.

In Set A, visits were conducted weekly for the 8-week treatment phase and the following assessments were occurred:

Adverse events (AEs)/serious AEs (SAEs): subjects and/or the parent(s)/legal guardian(s) were contacted by telephone at Weeks 5 and 7 to assess tolerability and to review AEs and concomitant treatment. Safety was monitored through the second follow-up visit (Week 13) or at Week 8 for those subjects entering the 6-month open-label extension study.

Hematology and blood chemistry evaluations: collected at the screening, Week 8 and/or Early Termination (ET) visits.

Liver function tests, Serum lipids, serum creatinine, blood urea nitrogen or urea: collected at the Week 4 study visit.

Urinalysis: collected at the screening, Weeks 4 and 8 and/or ET visits as appropriate. Urine was collected to test for pH, specific gravity, glucose, blood, ketones, and protein.

Physical examination: a physical examination and Tanner assessment were completed at the screening, Week 8 and/or ET visits as appropriate.

Vital signs: assessed at the screening, baseline (Day 1), Weeks 1, 2, 3, 4, 6, 8, 9, 11, unscheduled, and ET visits as appropriate. Temperature and respiratory rate were assessed at screening and Week 8. A 12-lead electrocardiogram (ECG) was performed at the screening, baseline, Week 8 and/or ET visits.

Columbia-Suicide Severity Rating Scale (C-SSRS): evaluated at the screening, baseline (Day 1), Weeks 1, 2, 3, 4, 6, 8, 9, 11, unscheduled and/or ET visits as appropriate.

In Set B, in addition to the assessments which occurred above in the placebo controlled studies, the following assessments occurred during the open label extension studies. Visits occurred on Days 7, 14, 21, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168, and 182 during the three extension trials.

Adverse events (AEs)/serious AEs (SAEs): collected at each visit through Week 30.

Hematology and blood chemistry evaluations: collected at Week 14 and Week 26 and/or Early Termination study visits as appropriate.

Blood chemistry evaluations: this included sodium, potassium, chloride, glucose, total carbon dioxide (CO2) or bicarbonate (HCO3), blood urea nitrogen (BUN) or urea, creatinine, calcium, phosphorus, uric acid, total bilirubin, prolactin, total

protein, albumin, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides, aspartate aminotransferase (AST) or serum glutamic-oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT) or serum glutamic pyruvate transaminase (SGPT), gamma glutamyltranspeptidase (GGT), alkaline phosphatase (AP) at Week 14, Week 26, and/or Early Termination study visits as appropriate. Fasting was not required prior to blood sample collection.

Urinalysis: collected at Week 14, and Week 26 or Early Termination study visits as appropriate. Urine was tested for pH, specific gravity, glucose, blood, ketones, protein, and a microscopic evaluation.

Physical examination (PE): a physical examination and Tanner assessment were completed at the Week 26 study visit or the Early Termination study visit, as appropriate.

Vital signs: including height, weight, and blood pressure, were assessed at Weeks 1, 2, 3, 4, 6, 10, 14, 18, 22, 26, 27, 28, and 30 and at Early Termination study visits, as appropriate.

Columbia-Suicide Severity Rating Scale (C-SSRS): evaluated at Weeks 1, 2, 3, 4, 6, 10, 14, 18, 22, 26, 27, 28 and 30, Unscheduled and/or Early Termination/Discontinuation study visits as appropriate.

7.2.5 Metabolic, Clearance, and Interaction Work

See Section 4.4.3 Pharmacokinetics.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Columbia Suicide-Severity Rating Scale (C- SSRS) was used to detect suicidal ideation and suicidal behavior because suicide is a class risk for antidepressants in the pediatric population. Other safety topics of special interest, based on a pediatric data review in conjunction with the known safety profile of DVS SR and venlafaxine, included an evaluation of adverse events such as mydriasis, blood pressure increases, cholesterol increases, body weight changes, decreased appetite, aggression, anger, homicidal ideation, hypomania or mania, and abnormal bleeding.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths of any of the subjects in the pediatric program clinical studies submitted in support of this Supplement. One fetal death occurred in a 17-year-old female who became pregnant while receiving DVS-SR 50 mg. The drug was tapered and stopped on July 22, 2014. The miscarriage occurred (b) (6), and a D&C was done (b) (6).

7.3.2 Nonfatal Serious Adverse Events

In Set A, a total of 10 (1.7%) subjects reported Serious Adverse Events (SAEs). The incidence of SAEs were comparable between treatment groups: 3 (1.3%) in the placebo, 3 (2.5%) in the DVS SR low dose, and 4 (1.7%) in the DVS SR high dose treatment group. In Set B, a total of 36 (5.3%) subjects reported SAEs. The most frequent SAEs from Set B were: Suicide attempt 10 (1.5%), Suicidal ideation, 7 (1.0%), Aggression 5 (0.7%), Auditory Hallucination 3 (0.4%), Agitation 2 (0.3%), Appendicitis 2 (0.3%), and Suicidal behavior 2 (0.3%).

A generalized tonic-clonic seizure occurred in a 14-year-old male who had no prior history of seizures. This subject had a past medical history of asthma and a past traumatic injury to left eye. A generalized tonic clonic seizure occurred while taking 50 mg of DVS SR, while on Day 106 of study. The seizure lasted approximately 1 to 2 minutes, and was followed by a post-ictal phase. The event was assessed as being due to the study drug.

Ketoacidosis occurred in a 14-year-old black male with a history of diabetes. (Subject 10231010) This patient had been on DVS-SR 25 mg for 67 days when he developed diabetes with weight loss and was treated with insulin.

One 17-year-old subject, (B206104- 11061006), had a positive pregnancy test at the final visit of the treatment phase. At that time, she was taking 35 mg DVS SR, and had completed 56 days of DVS-SR treatment. The subject was immediately withdrawn from the study but completed follow up. Post-study, the subject experienced postpartum hemorrhagic anemia, endometriosis, and postpartum hemorrhage following delivery of a full-term infant.

Table 8 Non-fatal Serious Adverse Events (Set A) Data	
Placebo	Suicidal ideation, dermatomyositis, suicide attempt
Low Dose DVS	Aggression, suicidal attempt, homicidal ideation, suicidal ideation
High Dose DVS	Suicidal ideation, postpartum hemorrhage and anemia, disinhibition, appendicitis with abscess

Table 9 Non-fatal Serious Adverse Events (Set B) Not Included in Table 8	
Placebo/DVS SR	Major depression, irritability, hallucination, euphoric mood, insomnia, self-injurious behavior
Fluoxetine / DVS	Asthma
DVS SR only	Suicidal behavior, ketoacidosis, anger, endometritis, fetal death, generalized tonic-clonic seizure pyromania, homicidal ideation, mania, femur fracture, bronchial hyperactivity, ovarian cyst

7.3.3 Dropouts and/or Discontinuations

Discontinuations due to Adverse Events (AEs): In Set A, the number (%) of subjects reporting AEs that led to discontinuation were: 9 (3.9%) subjects in the placebo, 7 (5.7%) in the low dose, and 5 (2.1%) in the high dose group. Overall the number of subjects who discontinued due to an AE were: 21 (3.6%) in Set A and 61 (8.9%) in Set B. The most frequently reported AEs causing discontinuation of treatment ($\geq$0.5%) in Set B were: Suicide attempt 1.0% (7 subjects), Irritability 1.0% (7 subjects), Suicidal ideation 0.9% (6 subjects), and Aggression 0.6% (4 subjects).

I examined the Integrated Summary of Safety Table 14.3.1.1.1.A1, which provided information on subjects reporting adverse events which caused discontinuation of treatment from the Set A Safety Population. None of the events occurred at a rate of 1% or greater except depression, which occurred at a rate of 1.3% in the placebo group. The following events each led to a dropout of one person in the group receiving any dose of DVS-SR: palpitations, mydriasis, vomiting, headache, sedation, aggression, disinhibition, hypomania, suicidal ideation, suicide attempt, dermatitis allergic, and rash macular.

7.3.4 Significant Adverse Events

No other significant adverse events were reported.

7.3.5 Submission Specific Primary Safety Concerns

The Columbia-Suicide Severity Rating Scale did not indicate any signal of concern. In Set A, suicidal ideation was reported in 10% of subjects in the placebo group, 8% subjects in the DVS SR low dose group, and 10% of subjects in the DVS SR high dose group based on C-SSRS data. Suicidal behavior was reported in 0.4% of subjects in the placebo group, 0.8% of subjects in the low dose group, and 0.0% subjects in the high dose group. In Set B, suicidal ideation was reported in 12.3% and suicidal behavior was reported in 1.2% of patients treated with DVS SR in both short-term and long-term studies. The latter figures are difficult to interpret without a placebo arm for comparison.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The only common, drug-related adverse events (occurring in at least 5% of subjects in either DVS group and at least twice the placebo rate) were headache, fatigue, and vomiting. Adverse events occurring at an incidence of ≥2% in either DVS SR group are listed in Table 10 below.

Table 10 TEAEs With Incidence ≥ 2% from Phase 3, Double-Blind, Placebo-Controlled Studies of DVS SR – B2061014 and B2061032

System Organ Class - Preferred Term	Placebo (N = 232) n (%)	DVS SR Low Dose (N = 122) n (%)	DVS SR High Dose (N = 236) n (%)
Subjects with Any Treatment Emergent Adverse Events	152 (66)	81 (66)	150 (64)
Gastrointestinal disorders			
Abdominal pain*	21 (9)	11 (9)	32 (14)
Diarrhea	5 (2)	3 (3)	8 (3)
Nausea*	19 (8)	12 (10)	24 (10)
Vomiting	8 (3)	1 (1)	14 (6)
General disorders and administration			
Fatigue	4 (2)	4 (3)	11 (5)
Orthostatic Hypotension*	2 (1)	4 (3)	4 (2)
Pyrexia*	0	3 (2)	0
Tachycardia*	1 (<1)	2 (2)	2 (<1)
Investigations			
Blood triglycerides increased	2 (1)	2 (2)	1 (<1)
Weight decreased	4 (2)	2 (2)	5 (2)
Infections and Infestations			
Gastroenteritis viral	42 (18)	19 (16)	39 (17)
Upper respiratory tract infection*	7 (3)	1 (<1)	2 (<1)
Metabolism and nutrition disorders	0	2 (2)	5 (2)
Decreased appetite	0	2 (2)	1 (<1)
Musculoskeletal and connective tissue			
Arthralgia	2 (1)	0	4 (2)
Back Pain	9 (4)	5 (4)	13 (6)
Muscle Spasms	46(20)	23 (19)	44 (16)
Pain in Extremity	9 (4)	4 (3)	4 (2)
Nervous system disorders			
Dizziness	2 (1)	2 (2)	2 (<1)
Headache*	5 (2)	12 (10)	9 (4)
Sedation*	4 (2)	6 (5)	1 (<1)
Psychiatric disorders			
Aggression	6 (3)	5 (4)	4 (2)
Irritability	6 (3)	2(2)	7 (3)
Insomnia*	152 (66)	81 (66)	150 (64)
Suicidal ideation and behavior*	8 (3)	6 (5)	5 (2)
Respiratory, thoracic and mediastinal disorders	5 (2)	3 (2)	8 (2)
Cough	19 (8)	12 (10)	24 (10)

See Appendix 9.4 for list of combined terms (designated by *).

7.4.2 Laboratory Findings

I examined the proportions of patients who met outlier criteria and mean changes from baseline to final on-therapy value for lab parameters.

Outliers of selected clinical parameters of interest were evaluated, and included information about blood glucose, alanine aminotransferase, bicarbonate, bilirubin, calcium, HDL and LDL cholesterol, prolactin, triglycerides, urate, hematocrit, hemoglobin, leukocytes as well as urine hemoglobin, ketones, specific gravity, glucose, and protein. These were examined using the Integrated Summary of Safety tables to evaluate for a higher incidence of outliers in either DVS SR group compared to placebo. No substantial differences from placebo were identified.

Because elevations in cholesterol were noted in studies of pediatric patients treated with venlafaxine, mean changes in cholesterol associated with DVS SR treatment were examined within Set A. There did not appear to be any large effect on the mean levels of cholesterol, HDL, or triglycerides relative to placebo, as noted in Table 11, 12, and 13, respectively. Final on-therapy refers to the last non-missing data during on-therapy period.

Table 11 Average Change in Cholesterol [MG/DL] From Beginning of Treatment in Double-blind, Placebo-controlled Studies of DVS-SR (Set A)

	Placebo Mean Δ n	DVS SR low dose Mean Δ n	DVS SR High dose Mean Δ n
2 Pooled Studies, 8 weeks/final on therapy	-3.5 N=212	-2.6 N=114	0.01 N=214

Table 12 Average Change in HDL Cholesterol from Beginning of Treatment in Double-blind, Placebo-controlled Studies of DVS-SR (Set A)

	Placebo Mean Δn	DVS SR low dose Mean Δn	DVS SR High dose Mean Δn
2 Pooled Studies, 8 weeks/final on therapy	-2.1 N=212;	-0.6 N=114;	-0.01 N=214;

Table 13 Average Change in Triglycerides [MG/DL] from Beginning of Treatment in Double-Blind, Placebo-controlled Studies of DVS-SR (Set A)			
	Placebo Mean Δn	DVS SR low dose Mean Δn	DVS SR High dose Mean Δn
2 Pooled Studies, 8 weeks/final on therapy	3.7 N=212	8.4 N=114	6.0 N=214

7.4.3 Vital Signs

The effect of DVS-SR on vital signs, weight, and height in the pediatric program are summarized in Tables 14 through Table 18 below. There were no new safety signals related to vital signs.

Table 14 Number of Subjects Identified Associated with Vital Signs of Potential Clinical Importance/Number of Subjects Tested – All Subjects – Set A - Safety Population on Therapy			
	Placebo n/N* (%)	DVS SR low dose n/N* (%)	DVS SR high dose n/N* (%)
Diastolic BP decrease of ≥15 mmHg from supine to standing	11/231 (4.8)	4/120 (3.3)	8/236 (3.4)
Diastolic Blood Pressure (mmHg) - Supine - Elevation at three consecutive visits	1/231 (0.4)	0/120 (0.0)	0/236 (0.0)
Pulse Rate (beats/min) – Orthostatic Increase of ≥20 bpm from supine to standing	84/231 (36)	47/120 (39)	89/236 (38)
Systolic Blood Pressure (mmHg) – Orthostatic Decrease of ≥20 mmHg from supine to standing	9/231 (3.9)	2/120 (1.7)	16/236 (6.8)
Systolic Blood Pressure (mmHg) -SUPINE - Elevation at three consecutive visits	0/231 (0.0)	0/120 (0.0)	2/236 (0.8)
Temperature (C) ≥101 °F and Increase from Baseline of ≥2°F	0/218 (0.0)	0/113 (0.0)	1/219 (0.5)

Low dose DVS SR was associated with a small decrease in body weight in placebo-controlled trials in pediatric patients with MDD (Table 15). There appeared to be an increased risk of weight loss when DVS-SR was compared to placebo (Table 16). The incidence of weight loss (≥3.5% of baseline weight) was 22%, 14%, and 7% for patients treated with low dose DVS-SR, high dose DVS-SR, and placebo, respectively. This did not appear to be completely due to anorexia as the reporting rates of decreased appetite were considerably less. There were no subjects who discontinued therapy because of weight loss or decreased appetite.

Table 15 Average Change in Body Weight (kg) From Beginning of Treatment in Double-blind, Placebo-Controlled Studies of DVS-SR (Set A)

	Placebo Mean Δn	DVS SR low dose Mean Δn	DVS SR High dose Mean Δn
2 Pooled Studies, 8 weeks/Final on therapy	0.59 n=231	-0.11 n= 120	0.24 n=236

Table 16 Number of Subjects Identified Associated with Weight Change from Baseline/Number of Subjects Tested – All Subjects – Set A - on therapy

	Placebo n/N* (%)	DVS SR low dose n/N* (%)	DVS SR high dose n/N* (%)
Weight gain (7% or more)	6/231 (3)	2/120 (2)	12/236 (5)
Weight Loss (3.5% or more)	16/231 (7)	26/120 (22)	34/236 (14)

The risks associated with longer term DVS SR use were assessed in 6-month, open-label extension studies in children and adolescents with MDD (Tables 17 and 18, respectively). Both children and adolescents treated for at least 6 months had mean changes in weight and height that approximated expected changes, based on data from age- and sex-matched peers.

Table 17 Change from baseline at Last On-Therapy Time Point for Z-Scores Relative to Normal Growth or Weight for Children - Set B (DVS SR Exposure Only), N=81

Time-point	Mean weight (SD)	Mean height (SD)
Baseline	0.9390 (1.1096)	0.6235 (0.9605)
Final on-therapy	0.9294 (1.0979)	0.5280 (0.9509)
Change from baseline to final on-therapy	-0.0148 (0.2624)	-0.1124 (0.3055)

Table 18 Change from Baseline at Last on-Therapy Time Point for Z-Scores relative to normal growth and weight for Adolescents - Set B - (DVS SR Exposure Only), N=142		
Time-point	Mean weight (SD)	Mean height (SD)
Baseline	0.8625 (1.3070)	0.2129 (1.0637)
Final on-therapy	0.9048 (1.3215)	0.2347 (1.0585)
Change from baseline to final on-therapy	0.0207 (0.2767)	0.0020 (0.2425)

7.4.4 Electrocardiograms (ECGs)

I examined EKG parameters including the number of outlier subjects in regards to rhythm, PR interval, QRS interval, QTcB, QTcF and rate. These data from the integrated summary of safety did not reveal any safety concerns. I also evaluated the EKG data set in JMP for QTc interval >500ms. No subjects had a QTcB > 500 ms or QTcF > 500 ms.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

No new information was submitted in this supplement.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

I examined the relationship between the incidence of the adverse events and the dose of DVS SR, using data in the integrated summary of safety tables, and found none.

7.5.2 Time Dependency for Adverse Events

The time course of adverse events in the pediatric program was not analyzed.

7.5.3 Drug-Demographic Interactions

There were no relationships noted between demographic factors and the incidence of adverse events examining age, sex and race in the integrated summary of safety tables.

7.5.4 Drug-Disease Interactions

These issues were part of the initial NDA and were not addressed in this efficacy supplement.

7.5.5 Drug-Drug Interactions

These issues were part of the initial NDA and were not addressed in this efficacy supplement.

7.6 Additional Safety Evaluations

None.

7.6.1 Human Carcinogenicity

No new information was provided.

7.6.2 Human Reproduction and Pregnancy Data

Data to support the Pregnancy and Lactation labeling Rule (PLLR) conversion of Pristiq labeling were rolled into this supplement and are currently under review by the Maternal Health Team in the Division of Pediatrics and Maternal Health. I will review this information in an addendum to this review.

7.6.3 Pediatrics and Assessment of Effects on Growth

Effects on growth are addressed in Section 7.4.3 above.

Evaluation of the changes in Tanner Stage did not reveal any concern. I reviewed tables of the shift from baseline to last assessment of Tanner staging assessment scores for boys and girls by age group and mean daily dose in both Set A and Set B from the ISS tables. A review of Tanner staging assessment scores for the overall populations in Set A and Set B did not identify a safety concern with respect to sexual maturation in pediatric MDD patients treated with DVS SR. In Set B, regressions in sexual maturity assessment scores were reported for 4 subjects in the pediatric program; however medical history and results of other growth parameters including height and weight for these 4 subjects was unremarkable. There were no AEs reported related to pubertal delay or disorders of puberty in the program. There were no new safety signals or concerns in regards to the impact on sexual maturity in pediatric MDD patients treated with DVS SR. A limitation of this assessment is the relatively brief duration of these trials relative to the time course for sexual maturation.

The Pediatric Review Committee (PeRC) met on December 13, 2017, to discuss this supplement. The PeRC agreed that the Applicant has fulfilled PMC #1229-1 to conduct two studies under PREA to assess the safety and effectiveness of DVS SR as a treatment for MDD in children and adolescents. They also agreed with the Applicant's request for a waiver of PMR #2053-1 to assess the efficacy of DVS SR in the maintenance treatment of patients ages 7 through 17 years with MDD because the trials in this supplement failed to demonstrate a meaningful therapeutic benefit.

7.6.4 Overdose, Drug Abuse, Withdrawal and Rebound

Information on overdoses from published literature is described in Section 9.1. Otherwise, no new information was identified with respect to overdose, drug abuse, withdrawal, or rebound effects.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

The cumulative review of the Sponsor's postmarketing desvenlafaxine pediatric case series through November 30, 2016 did not identify any new safety signals or concerns for the use of desvenlafaxine in pediatric patients.

9 Appendices

9.1 Literature Review/References

The Applicant searched the Embase Daily Alerts, and Embase databases cumulatively through 02 December 2016 for DVS safety-related information reported in the pediatric age category of <18 years. Individual case reports were excluded. The search for venlafaxine literature was performed in the following databases: The search used key words including: adverse drug reaction, toxicity, intoxication, hypersensitivity, safety, and side effect. The literature review conducted by the Applicant yielded 265 results, of these, 6 were identified as relevant.

Two open label studies of DVS in a MDD pediatric population were described, and these showed that DVS was generally well tolerated, and that the treatment emergent

adverse event rates were highest for the highest dose groups.[1,2] Several retrospective observational studies were done which reported on cases of DVS overdoses. In one case series of 79 patients, it was evident that DVS causes moderate-to-severe serotonin toxicity only when consumed in a very large dose or in association with other serotonergic agents.[3] In a study of 182 overdose cases, severe effects appeared to be associated with co-ingestants, and the risk of seizures or serotonin toxicity was low.[4] A study of accidental ingestion of DVS (up to 1000mg) in 56 children, age 11 months to 6 years, only 8 required hospital admission and only ~10% had any symptoms; all had good outcomes.[5]

The review of published literature did not identify any new safety signals or concerns in pediatric patients. DVS overdose did not frequently produce serious adverse effects. No regulatory action is needed based on the findings.

9.2 Labeling Recommendations

9.2.1 Labeling Recommendations related to PREA (PMC 1229-1)

The following text was recommended for addition to the Pristiq label in Section 8.4, Pediatric Use:

> Efficacy was not demonstrated during two adequate and well controlled, 8-week, randomized, double-blind, placebo-controlled, parallel group studies conducted in 587 patients (7 to 17 years of age) for the treatment of MDD.
>
> Antidepressants, such as PRISTIQ, increase the risk of suicidal thoughts and behaviors in pediatric patients *[see the Boxed Warning and Warnings and Precautions (5.1)]*.
>
> PRISTIQ was associated with a decrease in body weight in placebo-controlled trials in pediatric patients with MDD. The incidence of weight loss (≥3.5% of

[1] Findling RL, Groark J, Chiles D, et al. Safety and tolerability of desvenlafaxine in children and adolescents with major depressive disorder. J Child Adolesc Psychopharmacol 2014;24(4):201-9.

[2] Findling RL, Groark J, Tourian KA, et al. Pharmacokinetics and tolerability of single- ascending doses of desvenlafaxine administered to children and adolescents with major depressive disorder. J Child Adolesc Psychopharmacol 2016;26(10):909-21.

[3] Vlad IA, Armstrong JM. Toxicity of desvenlafaxine in overdose. Clin Toxicol 2015;53(4):392 (Abstr 342).

[4] Cooper JM, Brown JA, Cairns R, et al. Desvenlafaxine overdose and the occurrence of serotonin toxicity, seizures and cardiovascular effects. Clin Toxicol 2017;55(1):18-24.

[5] Chaney P, Morgan D, Borys DJ. Clinical effects of acute desvenlafaxine (Pristiq) ingestion by young children. Acad Emerg Med 2011;18(5)(Suppl 1):S73 (Abstr 182).

baseline weight) was 22%, 14%, and 7% for patients treated with low dose PRISTIQ, high dose PRISTIQ, and placebo, respectively.

The risks associated with longer term PRISTIQ use were assessed in 6-month, open-label extension studies in children and adolescents with MDD. Both children and adolescents had mean changes in weight that approximated expected changes, based on data from age- and sex-matched peers.

In clinical trials, exposure to desvenlafaxine was similar in adolescent patients 12 to 17 years of age, and was about 30% higher in pediatric patients 7 to 11 years of age.

9.2.2 Labeling Recommendations related to PLLR conversion

We 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 are pending at this time. Significant issues will be discussed in an addendum added to this review as appropriate.

PLLR conversion will address the following:

8.1 Pregnancy

- *Deletion of the letter category previously used to designate risk.*
- *Addition of the Pregnancy Registry contact info.*
- *Review of published literature: Although there was minimal data on desvenlafaxine, data on venlafaxine, the parent compound was proposed for addition to this section. Background risk information in the general population should be added as appropriate for the PLLR conversion.*
- *Under the Clinical Considerations heading, the Disease-associated maternal and/or embryo/fetal risk subheading was added.*
- *Under the Human Data heading, a summary of findings of published data will be added.*

8.2 Lactation

- *Information on lactation will be added to replace old regulatory language with new PLLR breastfeeding benefit-risk statement*

(b) (4)

9.3 Advisory Committee Meeting

No advisory committee meeting was required for this supplement.

9.4 Categorization of Adverse Events (Combined terms)

The following terms for similar conditions were combined as noted in Table 19, below, to facilitate the analysis of Adverse events.

Table 19 Categorization of Adverse Events

Common Term	Subsumed Preferred Terms
Orthostatic hypotension	Blood pressure orthostatic abnormal Orthostatic heart rate response increased Orthostatic hypotension
Tachycardia	Heart rate increased Tachycardia
Upper respiratory tract infection	URI Influenza Nasal congestion Nasopharyngitis Oropharyngeal pain Otitis media Otitis media acute Pharyngitis Pharyngitis streptococcal Rhinitis allergic Rhinorrhoea Sinus congestion Sinusitis Sneezing Upper respiratory tract congestion Upper respiratory tract infection Viral infection Viral upper respiratory tract infection
Abdominal pain	Abdominal discomfort Abdominal pain Abdominal pain lower Abdominal pain upper
Nausea	Dyspepsia Nausea
	Hyperthermia Pyrexia
Pyrexia	Aggression Agitation Anger Homicidal ideation Screaming
Suicidal Ideation and Behavior	Intentional self-injury Self injurious behavior Suicidal ideation Suicide attempt

Insomnia	Initial insomnia Insomnia Middle insomnia
Abnormal dreams	Abnormal dreams Nightmare
Sedation	Sedation Somnolence
Headache	Headache Migraine Sinus headache

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/s/

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