CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211964
PDUFA Goal Date	April 3, 2021
OSE RCM #	2019-2306
Reviewer Name	Victoria Sammarco, Pharm.D., M.B.A.
Team Leader	Carolyn Tieu, Pharm.D., M.P.H.
Division Director	LaCivita, Cynthia, Pharm.D.
Review Completion Date	March 15, 2021
Subject	Memorandum to the Evaluation of Need for a REMS
Established Name	Viloxazine hydrochloride
Trade Name	Qelbree
Name of Applicant	Supernus
Therapeutic Class	norepinephrine reuptake inhibitor
Formulation	extended release capsules
Dosing Regimen	Patients ages 6-11 years: 100 mg to 400 mg once daily Patients ages 12-17 years: 200 mg to 400 mg once daily

The risk evaluation and mitigation strategy (REMS) review was completed by the Division of Risk Management (DRM) in the previous cycle and was submitted to DARRTS on November 4, 2020 (DARRTS reference ID: 4696669). DRM had determined that a REMS was not needed to ensure the benefits of Qelbree outweigh the risks. Labeling will be used to communicate the risks associated with Qelbree to prescribers and should aid prescribers in appropriate monitoring. There is no additional or new clinical information that changes the benefit: risk profile in the resubmission and the assessment has not changed. Therefore, a REMS is not necessary for Qelbree to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
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Application Type	NDA
Application Number	211964
PDUFA Goal Date	November 8, 2020
OSE RCM #	2019-2306
Reviewer Name(s)	Victoria Sammarco, Pharm.D., M.B.A.
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Team Leader	Carolyn Tieu, Pharm.D., M.P.H.
Division Director	LaCivita, Cynthia, Pharm.D.
Review Completion Date	November 3, 2020
Subject	Evaluation of Need for a REMS
Established Name	Viloxazine hydrochloride
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Qelbree (viloxazine) is necessary to ensure the benefits outweigh its risks. Supernus Pharmaceuticals submitted a New Drug Application (NDA) 211964 for viloxazine with the proposed indication of treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6-17 years of age. The major risk associated with viloxazine is suicidal ideation and behavior. Other risks observed in the clinical program include increases in diastolic blood pressure and heart rate, interaction with bipolar disorder, decreased weight gain, and somnolence. The

(b) (4)

Medication Guide should be a part of labeling as there were no safety issues that require a REMS for viloxazine.

DRM has determined that a REMS is not necessary to ensure that the benefits outweigh the risks of viloxazine. The major risks identified and characterized during this submission will be communicated through labeling. The risk of suicidal thoughts and behaviors will be given a boxed warning, similar to that of the other norepinephrine reuptake inhibitors. The risks (increases in diastolic blood pressure and heart rate, interaction with bipolar disorder, decreased weight gain, and somnolence) will be described in the *Warnings and Precautions* sections of labeling.

At the time of this review, the clinical review team concluded that the Applicant has submitted sufficient evidence of the safety and effectiveness of viloxazine and the benefit/risk framework favors approval of viloxazine for the treatment of ADHD in pediatric patients ages 6 to 17 years. However, this application will receive a complete response due to manufacturing concerns.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Qelbree (viloxazine) is necessary to ensure the benefits outweigh its risks. Supernus (Applicant) submitted a New Drug Application (NDA) 211964 for viloxazine with the proposed indication of the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 17 years of age. This application is under review in the Division of Psychiatry (DP).

2 Background

2.1 PRODUCT INFORMATION

Viloxazine is an oral selective norepinephrine reuptake inhibitor proposed for the treatment of ADHD in pediatric patients ages 6 to 17 years. The mechanism of action of viloxazine in ADHD is unclear though it is thought to be through norepinephrine reuptake inhibition. Qelbree is an extended release capsule of viloxazine with a mean half-life of approximately 7 hours. The dosage forms include extended release capsules of 100 mg, 150 mg, and 200 mg.

[a] Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

The proposed dosing for pediatric patients ages 6 to 11 years is a starting dosage of 100 mg once daily. Dosage may be titrated in increments of 100 mg (b) (4) at weekly intervals, based on patient response. The maximum recommended dosage is 400 mg once daily.

The proposed dosing for pediatric patients ages 12 to 17 years is a starting dosage of 200 mg once daily. Dosage may be titrated in increments of (b) (4) 200 mg weekly. Maximum recommended dosage is 400 mg once daily.[1]

The parent compound, viloxazine, was previously marketed in Europe and other nations as an immediate release product for major depressive disorder. The drug was marketed under the brand names Vivalan® (UK, Belgium, France, Germany, Czech Republic, Portugal), Vivarint® (Spain* vs Vivarin), and Vicilan® (Italy). All brands were eventually withdrawn from markets worldwide for business reasons.[2]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 211964 relevant to this review:

- 11/08/2019: NDA 211964 submission (b) (4) for the treatment of ADHD in pediatric patients 6-17 years of age received.
- 04/16/2020: A Mid-cycle meeting occurred between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that would require a REMS for viloxazine.
- 07/20/2020: Draft label sent to Applicant noting a Warning and Precaution related to bipolar disorder as a comorbidity.
- 08/06/2020: A Late-cycle meeting occurred between the Agency and the Applicant via teleconference. The Agency informed the Applicant that a boxed warning would be required to for the risks of suicidal thoughts and behaviors, as well as inclusion of increases in heart rate and blood pressure and decreased weight gain in the *Warnings and Precautions* section of the label. The Agency also informed the Applicant of the need for post-marketing requirements targeting the following populations: pregnant and lactating women, patients with hepatic insufficiency, and children ages 4-≤6 years.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

ADHD is the most common neurobehavioral disorder of childhood and affects 3-10% of children and 1-6% of adults in the United States.[b,3] ADHD is characterized by high levels of impulsivity, hyperactivity,

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

and inattention. Symptoms are present before the age of 7, are present in more than one setting, and involve at least moderate impairment of function in several domains.[4] There are three primary subgroups of ADHD: predominately inattentive, predominately hyperactive-impulsive, or combined. No single etiology has been identified for ADHD and it is thought to be caused by a combination of environmental, genetic, and biological factors. The disorder can profoundly affect the academic achievement, well-being, and social interactions of children.[5,c] In adults, ADHD can affect risk-taking behaviors leading to higher rates of criminal behavior, driving accidents, and substance abuse.[6] In addition, management of the condition with behavioral interventions, medication therapy, and physician visits pose a significant economic burden.

3.2 Description of Current Treatment Options

The current treatment approach for ADHD includes non-pharmacologic (behavioral therapy, classroom interventions) and pharmacologic therapies. Pharmacologic therapies include stimulants and nonstimulants with stimulants being first line. Stimulants options include amphetamine, dextroamphetamine, methylphenidate, dexmethylphenidate, and lisdexamfetamine. Nonstimulant options include selective norepinephrine reuptake inhibitors such as atomoxetine, and alpha$_2$ adrenergic receptor agonists such as guanfacine and clonidine.[6] See Table 1 in Section 10 for summary of current pharmacologic treatment options for ADHD.

4 Benefit Assessment

There were four pivotal Phase 3 studies (812P301, 812P302, 812P303, 812P304; total n=1391). All four studies were randomized, double-blind, placebo-controlled, multicenter, 3-arm, parallel-group, studies evaluating the efficacy of viloxazine. Two trials (812P301 and 812P303) were in children 6 to 11 years of age and two trials (812P302 and 812P304) were in adolescents 12 to 17 years of age. All four trials were used in the benefit assessment of viloxazine in the pediatric population.

The primary objective of the four studies was to evaluate the efficacy of viloxazine compared with placebo as measured by change from baseline to end of study (varying from 6-8 weeks) in ADHD symptoms assessed using the ADHD Rating Scale 5th Edition (ADHD-RS-5) total score.

The key secondary endpoints of the four studies included the Clinical Global Impression-Improvement (CGI-I) scale score at end of study, the change from baseline in the Conners 3-Parent Composite T-score (assesses ADHD and associated learning and emotional problems in children by parent) at end of study, and the change from baseline in the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) Total Average Score at end of study.

Children between 6 to 11 Years of Age

In Study 812P301, 477 children with ADHD between 6 to 11 years of age were randomized to viloxazine 100 mg daily (n=157), viloxazine 200mg daily (n=161), or placebo (n=159) for 6 weeks. The primary

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug

objective of the study was to evaluate the efficacy of viloxazine compared to placebo by measuring change from baseline at week 6 in ADHD symptoms assessed using the ADHD-RS-5 total score. The primary endpoint was met where the ADHD-RS-5 total score exhibited a statistically significant improvement in subjects treated with viloxazine 100 mg/day (p=0.0004) or viloxazine 200 mg/day (p<0.0001) compared to placebo. Both doses also showed a statistically significant improvement in the CGI-I.

In Study 812P303, 313 children with ADHD between 6 to 11 years of age were randomized to viloxazine 400 mg daily (n=102), viloxazine 200 mg daily (n=107), or placebo (n=104) for 8 weeks, including up to a three-week titration period. The primary objective of the study was measured by change from baseline at week 8 in ADHD symptoms assessed using the ADHD-RS-5 total score. The primary endpoint was met where the ADHD-RS-5-total score exhibited a statistically significant improvement in subjects treated with viloxazine 200 mg/day (p=0.0038) or viloxazine 400 mg/day (p<0.0063) compared to placebo. A statistically significant improvement in the CGI-I was also observed for both doses.

Adolescents between 12 to 17 Years of Age

In Study 812P302, 310 adolescents with ADHD between 12 to 17 years of age were randomized to viloxazine 200 mg daily (n=100), viloxazine 400 mg daily (n=106), or placebo (n=104) for 6 weeks including a one-week titration period. The primary objective of the study was measured by change from baseline at Week 6 in ADHD symptoms assessed using the ADHD-RS-5 total score. The primary endpoint was met where the ADHD-RS-5 total score exhibited a statistically significant improvement in subjects treated with viloxazine 200 mg/day (p=0.0232) or viloxazine 400 mg/day (p<0.0091) compared to placebo. A statistically significant improvement in the CGI-I was also observed for both doses.

In Study 812P304, 297 adolescents with ADHD between 12 to 17 years of age were randomized to viloxazine 400 mg daily (n=100), viloxazine 600 mg daily (n=100), or placebo (n=97) for 7 weeks, including 2 weeks of titration and 5 weeks of maintenance dosing. The primary objective of the study was measured by change from baseline at Week 7 in ADHD symptoms assessed using the ADHD-RS-5 total score. The primary endpoint was met where the ADHD-RS-5 total score exhibited a statistically significant improvement in subjects treated with viloxazine 400 mg/day (p=0.0082) but not with viloxazine 600 mg/day (p<0.0712) compared to placebo. (b) (4)

(b) (4)

The clinical reviewer concludes that the Applicant's studies of viloxazine demonstrated statistically significant efficacy compared to placebo for the 100 mg, 200 mg, and 400 mg doses in patients ages 6 to 11 years and for the 200 mg and 400 mg doses in patients ages 12 to 17 years.[d] The clinical

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

meaningfulness of the results is supported by the positive findings on the CGI-I across dose groups. Hence, there is substantial evidence of effectiveness to support approval of viloxazine (100 mg, 200 mg, 400 mg) for the treatment of ADHD in pediatric patients ages 6 to 17 years.

At the time of this review, the integrated review has not been finalized. Please refer to Martine Solages' clinical review for additional information.

5 Risk Assessment & Safe-Use Conditions

The safety database was comprised of 925 patients from the phase 3 studies used to establish efficacy. A phase 2 dose-finding study (Study 812P202), and an open-label safety extension (Study 812P310) were also reviewed. The phase 2 study included 193 patients exposed to up to 400 mg of viloxazine. The open-label safety extension study consisted of 1097 subjects and did not include controlled data, but long-term trends in vital signs, growth parameters, and laboratory assessments were examined. Non-clinical and European post-marketing data for viloxazine immediate release formulations were also reviewed.

The most commonly observed adverse reactions (≥5% and at least twice the rate of placebo) were somnolence (16.1%), decreased appetite (7.4%), and fatigue (6.4%).[1] No deaths occurred during the development program. Serious adverse events (SAEs) occurred in six patients in the younger age (6-11 years) group and four patients in the older age (12-17 years) group who received viloxazine. The most common SAEs in patients receiving viloxazine in the phase 3 placebo-controlled trials were suicidal ideation or behavior (3 patients) and syncope (3 patients). In the long-term safety extension study, 2.3% of patients who received viloxazine experienced SAEs with the most common being suicidal ideation, syncope, and seizure.

Seizure and adverse events possibly related to seizures (e.g. syncope) was considered an adverse event of special interest as there were reports in multiple animal species in nonclinical trials. However, no seizures were reported in the controlled phase 2 and phase 3 studies, though seizure history was part of the exclusion criteria. Three patients experienced seizures during the open-label safety extension study. In reviewing the case narratives, there was no clear association between viloxazine and the seizures experienced. Data from published literature and post-marketing databases collected from Europe were also insufficient to show causality of viloxazine and seizures reported. (b) (4) [redacted] .[1]

The risk of suicidal thoughts and behavior will be included in a boxed warning as required by the Agency. The safety issues to be included in the *Warnings and Precautions* section of labeling include increased BP and HR, screening patients for bipolar disorder at risk for activation of mania or hypomania, decreased weight gain, and somnolence.

5.1 Suicidal Thoughts and Behavior

The emergence of suicidal thoughts and behaviors in pediatric patients is a known class effect of norepinephrine reuptake inhibitors. During the clinical development, 12/1118 (1.2%) viloxazine–treated

patients who participated in the phase 3 clinical trials experienced suicidal ideation or behavior compared to 3/487 (0.6%) placebo-treated patients.[e] Patients who exhibited suicidal ideation or behaviors may or may not have had a prior history of mood disorders, nor reported other psychiatric events during the study. The review team endorses a boxed warning for this risk of suicidal ideation and behavior to inform healthcare professionals of this serious risk.

5.2 EFFECTS ON BLOOD PRESSURE AND HEART RATE

As with many adrenergic-acting agents, viloxazine may cause increases in HR and BP. Elevations of HR and diastolic BP were demonstrated in phase 3 trials. Elevations in HR occurred in 1.7% of patients treated with viloxazine (no patients in the placebo group). The mean change in HR in viloxazine-treated patients over the duration of studies was 4.2 bpm (standard deviation (SD)= 13 mmHg), compared with 0.4 bpm (SD=10.8 mmHg) in patients on placebo.

Patients receiving viloxazine on average showed an increase in diastolic BP by the end of their respective studies. The mean change from baseline in diastolic BP was 2.4 mmHg (SD=9.2) in all viloxazine-treated patients compared with 0.4 mmHg (SD=8.5) in patients on placebo. Patients receiving viloxazine also tended to have more clinically meaningful BP elevations (increase of ≥10 mmHg). Effects on HR and BP were dose dependent.

Providers will be warned of this risk in the *Warnings and Precautions* section of the label. Patients should be monitored before initiation, with dose changes and periodically.

5.3 SCREENING PATIENTS FOR BIPOLAR DISORDER

A class effect of noradrenergic drugs is that they may induce a manic or mixed episode in patients with bipolar disorder. Though no manic episodes occurred in the Qelbree clinical program, the class effect requires description in *Warnings and Precautions* in the label. Screening for bipolar disorder should occur before commencement of therapy.

5.4 EFFECTS ON WEIGHT

Patients receiving viloxazine were also more likely to have decreased appetite and decreased weight gain and, were more likely to lose weight than patients receiving placebo. In Phase 3 trials, the average change from baseline weight in viloxazine-treated patients was 0.2 kg in patients ages 6 to 11 years (compared to 1 kg in the placebo group). In patients ages 12-17, the average change from baseline weight in viloxazine-treated patients was -0.2 kg (compared to 1.5 kg gained in the placebo group). Long term data is needed to understand the persistence of viloxazine's ability to cause decreased weight on growth trajectory in pediatric patients but this risk will appear in the *Warnings and Precautions* section of the label.

[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

5.5 SOMNOLENCE

Somnolence is a commonly observed adverse event of norepinephrine reuptake inhibitors and was the adverse event of greatest frequency in the Qelbree clinical program affecting 16% of viloxazine-treated patients (4% in placebo). Patients will be warned that viloxazine may impair patient's ability to drive or operate heavy machinery. This risk will appear in the *Warnings and Precautions* section of the label.

Post marketing requirements will also be required and focused on viloxazine in pregnancy and lactation, hepatic impairment and in children ages 4 to ≤ 6 years.

At the time of this review, the integrated review has not been finalized. Please refer to Martine Solages' clinical review for additional information on the risks associated with viloxazine.

6 Expected Postmarket Use

ADHD is the most common neurobehavioral disorder of childhood, affecting both children and adolescents with symptoms and/or sequelae reaching into adulthood. The likely prescribers for viloxazine are pediatricians, general practitioners, and psychiatrists. Viloxazine will likely be primarily prescribed and administered in an outpatient setting. ADHD is a chronic disease of childhood and adolescence and the duration of treatment is expected to be long-term.[f]

7 Risk Management Activities Proposed by the Applicant

(b) (4) The MG addressed the following risks: suicidal thoughts, monoamine oxidase inhibitor (MAOI) contraindications, need for dose adjustments in renally impaired patients, pregnancy risks, and common adverse events. At the Mid-Cycle Meeting held between the Agency and the Applicant on April 16, 2020, the Agency reiterated (b) (4) the Applicant is responsible for making the MG available for distribution to the patient, and the authorized dispenser of the product for which a MG is required must provide a MG directly to each patient (or to the patient's agent) when the product is dispensed. The risks associated with viloxazine were not deemed to require further risk mitigation beyond labeling and the Applicant was instructed that a REMS was likely not needed.

8 Discussion of Need for a REMS

The review team recommends a complete response (CR) of viloxazine due to manufacturing concerns. Certain facilities could not be inspected due to travel warnings stemming from COVID-19 and the

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Applicant could not provide documentation of procedures for handling laboratory records or appropriate re-qualification of analytical instruments. The review team otherwise concluded that the Applicant has submitted sufficient evidence of the safety and effectiveness of viloxazine and the benefit/risk framework favors approval of viloxazine (100 mg, 200 mg, (b) (4)) for the treatment of ADHD in patients ages 6 to 17 years. At the time of this review, the integrated review has not been finalized. Please refer to Martine Solage's clinical review for additional information.

Viloxazine is an extended release, oral selective norepinephrine reuptake inhibitor. An immediate release formulation of viloxazine was also marketed in Europe and other non-European countries for the treatment of depression.[2] Clinical efficacy is supported by four pivotal Phase 3 studies which showed statistically significant changes in ADHD-RS-5 scores from baseline. The clinical meaningfulness of the results is supported by the positive findings on the CGI-I across dose groups.

Viloxazine is similar to atomoxetine, another norepinephrine reuptake inhibitor indicated for pediatric ADHD, and numerous norepinephrine reuptake inhibitor antidepressants, such as duloxetine and bupropion, that have been on the market for many years. Norepinephrine reuptake inhibitors carry class risks of suicidality (boxed in most products), increases in HR and/or BP, decreased weight gain (atomoxetine), effects on bipolar disorder via activation of mania or hypomania, and somnolence that were observed in the clinical program. These risks are currently conveyed in the labeling of atomoxetine and various other norepinephrine reuptake inhibitor antidepressants such as duloxetine and bupropion.[7,8,9] None of these products are approved with a REMS.

Viloxazine's risks were not deemed to be more severe than those associated with other norepinephrine reuptake inhibitors. Other major risks outside of the drug's adrenergic activity were not identified. Hence, labeling for viloxazine is in line with marketed norepinephrine reuptake inhibitors. The risk of suicidal thoughts and behaviors will be given a boxed warning. Other risks (increases in diastolic BP and HR, interaction with bipolar disorder/activation of mania or hypomania, decreased weight gain, and somnolence) will be described in the *Warning and Precautions* section of labeling.[1] Additionally, the likely prescribers (pediatricians, general practitioners, and psychiatrists) should be familiar with class-wide risks associated with norepinephrine reuptake inhibitors and well-suited to escalate care as needed. Overall, the benefit-risk profile is favorable. Therefore, a REMS is not necessary for viloxazine to ensure the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on the initial clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for viloxazine to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 CURRENT PHARMACOLOGIC TREATMENTS

Table 1. FDA Approved Treatment Options for ADHD

Table 2. FDA Approved Treatment Options for ADHD **Product Name** *Proprietary Name* (established)	**Dosing/Administration**	**Important Safety and Tolerability Issues**	**Boxed Warnings**
Stimulants			
Evekeo *Evekeo ODT* *Adzensys ER* *Adzenys XR-ODT* *Dyanavel XR* (Amphetamine)	*Evekeo and Evekeo ODT*: 5 – 40 mg/day given in one to two divided doses *Adzenys ER and XR-ODT*: 6.3 – 18.8 mg/day *Dyanavel XR*: 2.5 – 20 mg/day	Drug dependence Serious cardiovascular reactions Psychiatric adverse reactions	-High potential for abuse -Misuse may cause sudden death and serious cardiovascular adverse events
Adderall XR *Mydayis* (Amphetamine/ Dextroamphetamine)	*Adderall XR*: 5-30 mg/day *Mydayis*: 12.5 – 50 mg	Drug dependence Serious cardiovascular reactions Psychiatric adverse reactions Tics	-High potential for abuse -Misuse may cause sudden death and serious cardiovascular adverse events
Focalin *Focalin XR* (Dexmethylphenidate)	*Focalin*: 5-20 mg/day in two divided doses *Focalin XR*: 5-40 mg/day	Serious Cardiovascular Events Psychiatric adverse reactions Long-term suppression of growth Visual Disturbance	-High potential for abuse
Dexedrine	*Dexedrine*: 5 – 40 mg/day *ProCentra*: 2.5 – 40	Serious Cardiovascular Events	-High potential for abuse

ProCentra *Zenzedi* (Dextroamphetamine)	mg/day in 2-3 divided doses *Zenzedi*: 2.5-40 mg/day in 2 – 3 divided doses	Psychiatric adverse reactions Visual Disturbance	
Vyvanse (Lisdexamfetamine)	30-70 mg/day	Potential for Abuse and Dependence Serious Cardiovascular Events Psychiatric adverse reactions Long-term suppression of growth	-High potential for abuse
Aptensio XR *Adhansia XR* *Concerta* *Cotempla XR-ODT* *Jornay PM* *Metadate ER* *Methylin* *QuilliChew ER* *Quillivant XR* *Ritalin* *Ritalin LA* (Methylphenidate)	*Aptensio XR*: 10-60 mg/day *Adhansia XR:* 25-85 mg/day *Concerta*: 18-72 mg/day *Cotempla XR-ODT*: 17.3 – 51.8 mg/day *Jornay PM:* 20-100mg/day *Metadate ER*: Ritalin – 5-60 mg/day in 2-3 divided doses *Methylin*: 5- 60 mg/day in 2-3 divided doses *QuilliChew ER*: 10-60 mg/day *Quillivant XR*: 20-60 mg/day *Ritalin*: 5-60 mg/day in 2-3 divided doses *Ritalin LA*: 20-60 mg/day	Serious Cardiovascular Events Psychiatric adverse events Long-term suppression of growth Visual Disturbance	-High Potential for abuse
Daytrana (Methylphenidate) transdermal	10-30 mg/day	Serious Cardiovascular Events Psychiatric adverse events Long-term suppression of growth	-High Potential for Abuse

		Visual Disturbance Chemical Leukoderma	
Selective Norepinephrine reuptake inhibitors (SNRI)			
Strattera (Atomoxetine)	Patients under 70 kg: 0.5 mg/kg/day – 1.2 mg/kg/day Patients over 70 kg: 40 - 100 mg/day	Suicidal Ideation Severe Liver Injury Serious cardiovascular reactions	-Increased risk of Suicidal Ideation
Alpha$_2$ Adrenergic Receptor Agonists			
Kapvay (Clonidine extended-release)	0.1-0.4 mg/day in two divided doses	Hypertension, bradycardia, and syncope Sedation and Somnolence Cardiac Conduction Abnormalities	NA
Intuniv (Guanfacine extended-release)	1 mg – 7 mg (0.05 -0.12 mg/kg) daily	Hypertension, bradycardia, and syncope Sedation and Somnolence Cardiac Conduction Abnormalities Rebound Hypertension	NA

10.2 REFERENCES

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