HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on October 20, 2023 via MS Teams. The meeting was called to order by Dr. Moron, Chair at 9:31 a.m.

Members

Member Names	Attendance	Member Names	Attendance
Yekini Adeyemi, RN	Absent	David Moron, MD- Chair	Present
Angela Babin, RPh	Present	Leah Nunez, PharmD	Absent
John Bennett, MD	Present	Teri Newsom, APRN	Present
Giovanna Betancourt, PharmD	Present	Brittany Parmentier, PharmD	Present
Rakesh Chadalavada, MD	Present	Kasey L. Pena, PharmD- Secretary	Present
German Corso, MD	Present	Kenda Pittman, PharmD	Present
Megan Cummings, APRN	Present	Sangeetha Rajan, MD	Present
Brad Fitzwater, MD	Present	Rishi Sawhney, MD	Absent
Catherine Hall, PharmD	Absent	Lesia Trickett, MD	Present
Dana Hopkins, RN	Absent	Ashton Wickramasinghe, MD	Present
Jeffery Matthews, MD	Absent	Patrick Young, MD	Absent

Guests Present: Tonya Barrios, State Hospitals Central Administration; Kristen Neumeister, PharmD, North Texas State Hospital, Wichita Falls; Joanne Anoje, PharmD, The Harris Center for Mental Health and IDD; Kayla Valigura, PharmD Candidate 2024, The University of Houston College of Pharmacy; Lisa Mican, PharmD, Austin State Hospital; Victoria Freberg, PharmD, Austin State Hospital; Bethany Whitaker, PharmD, Austin State Supported Living Center; Madeline Guidry, PharmD Candidate 2024, The University of Houston College of Pharmacy; Sovanarak Lek, PGY-5 Resident, Dell Medical School; Sharon Polackal, PGY-4 Resident, Dell Medical School; Samantha Nieto, Pharmacy Intern, UTEP School of Pharmacy

Opening

Introduction and Other Information

Dr. Pena introduced two new committee members:

- APRN Teri Newsom, Austin State Supported Living Center, as the new state supported living center APRN; and
- APRN Megan Cummings, North Texas State Hospital, Wichita Falls, as the new state hospital psychiatric APRN.

Conflict of Interest Disclosures

The committee members present did not disclose any new conflicts of interest.

Review of Minutes

The minutes from the July 28, 2023 meeting were approved as previously distributed.

Unfinished Business

None.

New Business

HHSC Psychiatric Drug Formulary Tables Annual Review

The committee reviewed and approved recommended revisions to the following tables:

- Psychotropic Dosage Guidelines
  - Ramelteon (Rozerem) Non-Formulary- added
  - Suvorexant (Belsomra) Non-Formulary- added
  - Tasimelteon (Hetlioz) Non-Formulary- added
- Therapeutic Serum Concentrations
- Reserve Drugs
  - Buprenorphine (Subutex [DSC])- removed
  - Buprenorphine/naloxone (Suboxone)- removed
  - Celecoxib (Celebrex)- removed

The updated formulary will be posted to the PEFC website.

Drug Information Templates

Medication Audit Criteria and Guidelines

The committee reviewed and approved revisions made to the Medication Audit Criteria and Guidelines template.

New Drug Application Form

The committee reviewed and approved revisions made to the New Drug Application Form.

New Drug Applications

Progesterone micronized (Prometrium)-pend

HHSC Legal Services provided guidance to the committee on the review and consideration of the NDA for Prometrium (progesterone) for potential gender therapy purposes in light of the passage of Senate Bill 14 during the 2023 Legislative

Session. After a thorough review of the evidence, the NDA will be considered at the next meeting.

Ofloxacin ophthalmic (Ocuflox®) and otic (Floxin®)-pend

Vortioxetine (Trintellix™)

Presented by Kayla Valigura, PharmD Candidate 2024. Please refer to Appendix A for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of Vortioxetine (Trintellix) to the formulary as a Reserve Drug in the Psychotropic Agents-Miscellaneous Antidepressants section.

The formulary check list was completed and no issues were detected.

HHSC Psychiatric Drug Formulary Annual Review

The committee reviewed and approved revisions to the 2024 HHSC Psychiatric Drug Formulary.

The updated formulary will be posted on the PEFC website.

Adverse Drug Reaction Reports

ADR: Hyponatremia/lamotrigine

A 26-year-old male admitted to the Psychiatric Hospital in March of 2022. Diagnoses include Schizoaffective disorder bipolar type, Autism spectrum disorder, Borderline intellectual functioning, history of dyslipidemia, history of hyponatremia secondary to divalproex and history of psychogenic polydipsia leading to mild hyponatremia. During the admission, he was reported to have polydipsia and seek fluids from every available source including the commode, and he was prescribed sodium chloride tablets due to multiple instances of mild hyponatremia. Lamotrigine was initiated in January 2023 and was titrated up. Four episodes of severe hyponatremia occurred over the next two months with sodium levels of 121-125 mmol/L, with one incidence of 115 mmol/L at a lamotrigine dose of 200mg/day. Reductions to various psychotropic medications were made but lamotrigine dose continued to be titrated up throughout this period. After the episode with the sodium level of 115 mmol/L, lamotrigine was tapered and discontinued with no further events of hyponatremia.

The most likely cause for the increasing severity of hyponatremia observed during this admission is likely a combination of ongoing psychogenic polydipsia as well as new initiation and titration of lamotrigine based on the timeline of events. Additionally, the addition of clozapine, which has been reported as a treatment for psychogenic polydipsia, appeared to have improved the patient's polydipsia, which could also contribute to improved sodium levels.

ADR: Intracranial/intraventricular hemorrhage/apixaban

A 58-year-old Caucasian female with a history of TBI, CVA, stroke, afib, and other medical complications has been admitted to the psychiatric hospital for over 6 years. She was taking apixaban for atrial fibrillation in addition to several psychotropic mediations and thyroid and cholesterol medications. In July 2023, the patient refused dinner and refused to get out of bed and had two episodes of non-bloody emesis. Upon observation, she was tachypneic with 26 breaths per minute, she then began to be slump over in her wheelchair and became unresponsive. After transfer to the medical hospital, MRI showed large volume acute intraventricular hemorrhage and moderate obstructive hydrocephalus with no evidence of acute brain ischemic infarct. Kcentra was administered to reverse apixaban. Over the next few days, the intracranial hemorrhage remained stable and based on neurology consult, it was thought to be highly unlikely that the patient would be able to ambulate or feed herself independently. A decision was made with her medical power of attorney and providers that the best care would be a one-way extubation. She was then extubated and transitioned to comfort measures and passed peacefully.

While intracranial hemorrhage is a known and uncommon adverse effect of apixaban therapy, it cannot be confirmed that the medication alone contributed to this adverse event given the patient's past history of a TBI, CVA, stroke, afib, and other medical complications.

ADR: Emesis/cyproheptadine

A 92-year-old Caucasian female resident of a state supported living center (SSLC) was started on cyproheptadine on 4/26/23 due to unexplained weight loss. The patient vomited on 4/27 and 5/9. She was hospitalized for aspiration pneumonia following the 5/9 emesis. Cyproheptadine was discontinued on 5/15 as patient does not have a history of emesis and the new events appeared to correlate with initiation of the new drug. There has been no recurrence of emesis since discontinuation of cyproheptadine.

Patient medical history includes severe intellectual development disability, bipolar disorder, pyloric stenosis, constipation, dementia, CKD stage 3b. Other medications include acetaminophen, ascorbic acid, aspirin, bisacodyl, cholecalciferol, clonazepam, cyanocobalamin, gabapentin, iron polysaccharide, levothyroxine, melatonin, Miralax, and fluoxetine.

Quarterly Non-Formulary Drug Justification Report

For the fourth quarter of fiscal year 2023 (June 2023 to August 2023), only the state hospitals reported use of non-formulary agents. The state supported living centers (SSLCs) currently do not have the capability to obtain non-formulary drug usage reports from their computer system but are working with the vendor to make this reporting possible. The following were the top six non-formulary agents, by number

of orders, that were prescribed in the state hospitals during the fourth quarter of fiscal year 2023:

- NAC
- Paxlovid
- Molnupiravir
- Gemfibrozil
- Ferrous gluconate
- Torsemide

Drug Formulary Sectional Review

In reviewing the formulary drug listings for Analgesics/Antipyretics and Anticonvulsants, the following changes were approved:

- Analgesics-Opiate Agonists
  - Morphine – remove sublingual tablet
- Added DSC to several discontinued brand name medications
- Updated Cost Index of several items

The updated formulary will be posted on the PEFC website.

Other Formulary Changes

The committee reviewed and approved the following changes:

- Vortioxetine (Trintellix) was added to the Antidepressant table in the Psychotropic Dosage Guidelines.
- Clarified the Therapeutic Reference Range for Lithium.

The updated formulary will be posted on the PEFC website.

Issues from the Chief Medical Officer, State Hospitals

Dr. Matthews was not present to present a report.

Issues from the Medical Services Coordinator, SSLCs

Dr. Wickramasinghe stated he learns a lot participating in this committee and noted the importance of psychiatry and medical providers meeting to discuss issues.

The SSLC's continue to go through positive changes related to the DOJ settlement.

Drug Shortages, Recalls, and FDA Safety Communications

The FDA has issued the following safety communications and recalls that may impact our facilities:

Shortages

The following medications are in shortage:

- Albuterol sulfate inhalation solution

- Amphetamine salt combos
- Amoxicillin oral powder for suspension
- Clonazepam
- Diazepam rectal gel
- Lidocaine injection
- Liraglutide (Victoza)
- Lisdexamfetamine (Vyvanse)
- Lorazepam injection
- Moxifloxacin tablet (NEW)
- Semaglutide (Ozempic, Wegovy)
- Sterile water for injection

Recalls

- Marlex Pharmaceuticals recalled digoxin tablets 0.125mg and 0.25mg due to label mix up.
- VistaPharm recalled sucralfate oral suspension due to microbial contamination.
- Hospira recalled lidocaine injection and sodium bicarbonate injection due to potential presence of glass particulates.

FDA Safety-related Communications and Labeling Changes

- Simvastatin: Added reports of new onset/exacerbation of myasthenia gravis.
- Rifampin: Rifampin is contraindicated in patients receiving lurasidone (rifampin is a strong CYP3A4 inducer and will cause decreased levels of lurasidone).
- Desvenlafaxine, venlafaxine, levomilnacipran, milnacipran, vilazodone, citalopram, escitalopram, fluoxetine, sertraline: Added information regarding a less than two-fold increased risk of postpartum hemorrhage related to exposure to SSRIs or SNRIs, particularly in the month before delivery.
- Carbamazepine: Added information regarding risk of increased plasma carbamazepine levels with concomitant use of olanzapine, dantrolene, or ibuprofen. Also added more information regarding carbamazepine's enzyme induction.

Open Forum

- Dr. Fitzwater brought up that there has been a rise in cases of congenital syphilis, however treatment may be complicated by a shortage of penicillin.
- Dr. Wickramasinghe stated a recent article indicated that many patients who self-report penicillin allergies are not truly allergic. Using the Pen-Fast Questionnaire, data shows 95% of people who report to be allergic to penicillin are not. Providers usually exclude penicillin because of self-reporting and order stronger antibiotics, which can present a challenge for Antibiotic Stewardship.

Next Meeting Date

The next meeting is scheduled for January 12, 2024.

Adjourn

There being no further business, the meeting was adjourned at 2:04 p.m.

Approved: *David Moron*

David Moron, MD, Chairman

Minutes Prepared by:
Tonya Barrios, PhTR
Reviewed by:
Kasey L. Pena, PharmD

Appendix A

Vortioxetine (Trintellix™)

Classification

Selective Serotonin Reuptake Inhibitor

Pharmacology[1]

The mechanism of the antidepressant effect of vortioxetine is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism.

Black Box Warning - Suicidal thoughts and behaviors

Antidepressants increase the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. Vortioxetine is not approved for use in pediatric patients.

Indication[1]

Vortioxetine is indicated for the treatment of major depressive disorder (MDD) in adults.

Pharmacokinetics[1]

Pharmacokinetic Parameter	Details
Absorption	The maximal plasma vortioxetine concentration (Cmax) after dosing is reached within 7 to 11 hours post dose (Tmax). Steady-state mean Cmax values were 9, 18, and 33 ng/mL following doses of 5, 10, and 20 mg/day. Absolute bioavailability is 75%. Food does not impact pharmacokinetics.
Distribution	The apparent volume of distribution of vortioxetine is approximately 2600 L, indicating extensive extravascular distribution. The plasma protein binding of vortioxetine in humans is 98%, independent of plasma concentrations. No apparent difference in the plasma protein binding between healthy subjects and subjects with hepatic (mild, moderate or severe) or renal (mild, moderate, severe, ESRD) impairment is observed.
Metabolism	Vortioxetine is extensively metabolized primarily through oxidation via cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 and subsequent glucuronic acid conjugation. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite, and poor metabolizers of CYP2D6 have approximately twice the vortioxetine plasma concentration of extensive metabolizers.

Pharmacokinetic Parameter	Details
Excretion	Following a single oral dose of [14C]-labeled vortioxetine, approximately 59% and 26% of the administered radioactivity was recovered in the urine and feces, respectively as metabolites. Negligible amounts of unchanged vortioxetine were excreted in the urine up to 48 hours. The presence of hepatic (mild, moderate or severe) or renal impairment (mild, moderate, severe and ESRD) did not affect the apparent clearance of vortioxetine.

Dosage/Administration[1]

- The recommended starting dose is 10 mg administered orally once daily without regard to meals.
- Dosage should then be increased to 20 mg/day, as tolerated, as higher doses demonstrated better treatment effects in trials conducted in the United States.
- The efficacy and safety of doses above 20 mg/day have not been evaluated in controlled clinical trials.
- A dose decrease down to 5 mg/day may be considered for patients who do not tolerate higher doses.
- Vortioxetine can be discontinued abruptly. However, it is recommended that doses of 15 mg/day or 20 mg/day be reduced to 10 mg/day for one week prior to full discontinuation if possible.
- The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers.

Use in Special Populations

- **Pregnancy:** Information specific to vortioxetine use in pregnancy is limited. As a class, SSRIs have been evaluated extensively in pregnant patients. Studies focusing on newborn outcomes following first trimester exposure often have inconsistent results due to differences in study design and confounders such as maternal disease and social factors. Adverse effects in the newborn following SSRI exposure late in the third trimester can include apnea, constant crying, cyanosis, feeding difficulty, hyperreflexia, hypo- or hypertonia, hypoglycemia, irritability, jitteriness, respiratory distress, seizures, temperature instability, tremor, and vomiting. Prolonged hospitalization, respiratory support, or tube feedings may be required. Symptoms may be due to the toxicity of the SSRIs or a discontinuation syndrome and may be consistent with serotonin syndrome associated with SSRI treatment.
- **Lactation:** Vortioxetine is present in breast milk.
    - Following a dose of vortioxetine 10 mg/day (n = 2), the maximum breast milk concentration was 13.89 ng/mL and occurred 7 hours after the dose. Based on this information, authors of the study calculated[2] the relative infant dose (RID) of vortioxetine to be 1.1%, providing an estimated daily infant dose via breast milk of 0.0017 mg/kg/day, based on the weight-adjusted maternal dose.[2]

    - Following a dose of vortioxetine 20 mg/day (n = 1), the maximum breast milk concentration was 52.32 ng/mL and occurred 5 hours after the dose. Based on this information, the authors of the study calculated the RID of vortioxetine to be 1.7%, providing an estimated daily infant dose via breast milk of 0.0052 mg/kg/day.[2]
    - In general, breastfeeding is considered acceptable when the RID of a medication is <10%.[2]
- **CYP2D6 Poor Metabolizers:** The maximum recommended dose of vortioxetine is 10 mg/day in known CYP2D6 poor metabolizers.[1,2]
- **Geriatric use:** No dose adjustment is recommended on the basis of age. Results from a single dose pharmacokinetic study in elderly (>65 years old) vs young (24 to 45 years old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.[1]

Contraindications[1]

- Vortioxetine is contraindicated in patients with hypersensitivity to vortioxetine or any components of the formulation. Angioedema has been reported in patients treated with vortioxetine.
- The use of MAOIs intended to treat psychiatric disorders with vortioxetine or within 21 days of stopping treatment with vortioxetine is contraindicated because of an increased risk of serotonin syndrome.
- The use of vortioxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated.

Precautions[1]

- Serotonin Syndrome has been reported with serotonergic antidepressants (SSRIs, SNRIs, and others), including with vortioxetine, both when taken alone, but especially when coadministered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort). If such symptoms occur, discontinue vortioxetine and initiate supportive treatment.
- If concomitant use of vortioxetine with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.
- Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when vortioxetine is coadministered with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation.
- Difficulties in sexual desire, sexual performance, and sexual satisfaction may be a consequence of treatment with vortioxetine. Since sexual dysfunction is known to be an underreported adverse effect, a validated measure designed to identify sexual side effects was used prospectively in seven placebo-controlled

trials. The results of these trials found that there was a dose related sexual dysfunction incidence of 22-34% in women and 16-29% in men.
- Some patients experienced discontinuation syndrome in the first week of abrupt discontinuation of vortioxetine 15 mg/day and 20 mg/day.
- Hyponatremia can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH).
- Angle Closure Glaucoma: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants.
- Activation of Mania/Hypomania can occur with antidepressant treatment. Screen patients for bipolar disorder.

Adverse Effects

- Nausea is the most common adverse reaction and dose related, with higher doses having a higher incidence (21-32%)[1]. Nausea commonly occurs within the first week of treatment, then decreases in frequency but can persist in some patients.[1]
- Discontinuation symptoms have been seen in the first week of abrupt discontinuation of vortioxetine 15 mg and 20 mg. Symptoms include headache, muscle tension, mood swings, sudden outbursts of anger, dizziness, and runny nose.[1]
- Other common adverse effects include adverse effects include constipation and vomiting. These occurred at $\geq$5% incidence and at least twice the rate of placebo.

Monitoring[2]

- Signs of worsening depression
- Suicidal ideations (especially at initiation of therapy or after dosing changes)
- Signs of new or worsening anxiety
- Social functioning
- New or worsening signs of mania
- Panic attacks
- Akathisia
- Signs/symptoms of serotonin syndrome
- Signs/symptoms of hyponatremia

Interactions

Drug Interactions	Example Medications	Clinical Impact	Management
Strong inhibitors of CYP2D6	Bupropion, fluoxetine, paroxetine, or quinidine	Strong CYP2D6 inhibitors may increase the serum concentration of vortioxetine which can enhance the serotonergic effect, thus there is a higher risk of serotonin syndrome.[2]	Reduce vortioxetine dose by half when a strong CYP2D6 inhibitor is coadministered.[1]
Strong CYP Inducers	Rifampin, carbamazepine, or phenytoin	CYP inducers may decrease the serum concentration of vortioxetine.[2]	Consider increasing the vortioxetine dose when a strong CYP inducer is coadminstered for more than 14 days. The maximum recommended dose should not exceed 3 times the original dose.[1]
Serotonergic Agents	SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products	Based on the mechanism of action of vortioxetine and the potential for serotonin toxicity, serotonin syndrome may occur when vortioxetine is coadministered with other drugs that may affect the serotonergic neurotransmitter systems.[1]	Closely monitor symptoms of serotonin syndrome if vortioxetine is coadministered with other serotonergic drugs. Treatment with vortioxetine and any concomitant serotonergic agents should be discontinued immediately if serotonin syndrome occurs.[1]
Highly Protein Bound Drugs	Warfarin*, aspirin, valproic acid	Vortioxetine is highly protein bound to plasma protein, coadministration of vortioxetine with other highly protein bound drugs may increase free concentrations of the other	Take caution with administering highly protein bound drugs with vortioxetine. Clinicians should refer to drug specific prescribing information for guidance on how to manage this interaction.

*** However, in a clinical study with coadministration of vortioxetine (10 mg/day) and warfarin (1 mg/day to 10 mg/day), a highly protein-bound drug, no significant change in INR was observed.[1]**

Efficacy[1]

Adults (aged 18 years to 75 years):

- The efficacy of vortioxetine in patients aged 18 years to 75 years was demonstrated in five, 6-to-8-week, placebo-controlled studies (Studies 1 to 5 in Table 1).
- In these studies, patients were randomized to vortioxetine 5 mg, 10 mg, 15 mg, 20 mg, or placebo once daily. For patients who were randomized to vortioxetine 15 mg/day or 20 mg/day, the final doses were titrated up from 10 mg/day after the first week.
- The primary efficacy measures were the Hamilton Depression Scale (HAMD-24) total score in Study 2 and the Montgomery-Asberg Depression Rating Scale (MADRS) total score in all other studies.
- In each of these studies, at least one dose group of vortioxetine was superior to placebo in improvement of depressive symptoms as measured by mean change from baseline to endpoint visit on the primary efficacy measurement (see Table 1).
- Subgroup analysis by age, gender or race did not suggest any clear evidence of differential responsiveness. Two studies of the 5 mg dose in the U.S. (not represented in Table 1) failed to show effectiveness.

Elderly Study (aged 64 years to 88 years):

- The efficacy of vortioxetine for the treatment of MDD was also demonstrated in a randomized, double-blind, placebo-controlled, fixed-dose study of vortioxetine in elderly patients (aged 64 years to 88 years) with MDD (Study 6 in Table 1).
- Patients met the diagnostic criteria for recurrent MDD with at least one previous major depressive episode before the age of 60 years and without comorbid cognitive impairment (Mini Mental State Examination score <24) received vortioxetine 5 mg or placebo.
- The primary efficacy measure in the elderly study was the Hamilton Depression Scale (HAMD-24) total score.
- As in the first 5 studies, at least one dose group of vortioxetine was superior to placebo in improvement of depressive symptoms as measured by mean change from baseline to endpoint visit on the primary efficacy measurement.

Table 1. Primary Efficacy Results of 6 Week to 8 Week Clinical Trials[1]

Study No. [Primary Measure]	Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference† (95% CI)
Study 1 [MADRS] Non-US Study	TRINTELLIX (5 mg/day)‡	108	34.1 (2.6)	-20.4 (1.0)	-5.9 (-8.6, -3.2)
	TRINTELLIX (10 mg/day)‡	100	34.0 (2.8)	-20.2 (1.0)	-5.7 (-8.5, -2.9)
	Placebo	105	33.9 (2.7)	-14.5 (1.0)	--
Study 2 [HAMD-24] Non-US Study	TRINTELLIX (5 mg/day)	139	32.2 (5.0)	-15.4 (0.7)	-4.1 (-6.2, -2.1)
	TRINTELLIX (10 mg/day)‡	139	33.1 (4.8)	-16.2 (0.8)	-4.9 (-7.0, -2.9)
	Placebo	139	32.7 (4.4)	-11.3 (0.7)	--
Study 3 [MADRS] Non-US Study	TRINTELLIX (15 mg/day) ‡	149	31.8 (3.4)	-17.2 (0.8)	-5.5 (-7.7, -3.4)
	TRINTELLIX (20 mg/day) ‡	151	31.2 (3.4)	-18.8 (0.8)	-7.1 (-9.2, -5.0)
	Placebo	158	31.5 (3.6)	-11.7 (0.8)	--
Study 4 [MADRS] US Study	TRINTELLIX (15 mg/day)	145	31.9 (4.1)	-14.3 (0.9)	-1.5 (-3.9, 0.9)
	TRINTELLIX (20 mg/day) ‡	147	32.0 (4.4)	-15.6 (0.9)	-2.8 (-5.1, -0.4)
	Placebo	153	31.5 (4.2)	-12.8 (0.8)	--
Study 5 [MADRS] US Study	TRINTELLIX (10 mg/day)	154	32.2 (4.5)	-13.0 (0.8)	-2.2 (-4.5, 0.1)
	TRINTELLIX (20 mg/day) ‡	148	32.5 (4.3)	-14.4 (0.9)	-3.6 (-5.9, -1.4)
	Placebo	155	32.0 (4.0)	-10.8 (0.8)	--
Study 6 (elderly) [HAMD-24] US and Non-US	TRINTELLIX (5 mg/day) ‡	155	29.2 (5.0)	-13.7 (0.7)	-3.3 (-5.3, -1.3)
	Placebo	145	29.4 (5.1)	-10.3 (0.8)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
† Difference (drug minus placebo) in least-squares mean change from baseline.
‡ Doses that are statistically significantly superior to placebo after adjusting for multiplicity.

Effect on Cognition[3]

- Randomized, double-blind, placebo-controlled trial to evaluate the effect of vortioxetine 10 mg and 20 mg compared to placebo on cognition function in adults aged 18-64 with recurrent MDD during a depressive episode of moderate severity or greater.
- Primary efficacy endpoint was change in the composition cognition score of the Digit Symbol Substitution Test (DSST) and the Rey Auditory Verbal Learning Test (RAVLT) from baseline to week 8.
- Both vortioxetine 10 mg and 20 mg were statistically significantly better than placebo in the primary efficacy measure ($p<0.0001$ for both doses).
- After statistically correcting for the effect on MADRS, both vortioxetine doses improved cognitive performance. This shows that the effect on cognitive function is independent of the effect on depression symptoms.
- The authors also completed a post-hoc analysis on non-responders (n=92) and non-remitters (n=68) and found that both vortioxetine doses improved cognitive performance in these two subgroups. The authors state that this

further supports the evidence that the effect on cognition is independent of the effect on depression.

Dosage Forms & Cost

Vortioxetine	Average Wholesale Price (30-day supply)	Price Per Tablet
5 mg IR tablets **10 mg IR tablets** **20 mg IR tablets**	$559.62	$18.65

Summary/Conclusion

Vortioxetine is a selective serotonin reuptake inhibitor FDA approved for the treatment of major depressive disorder (MDD) in adults. Clinical trials of vortioxetine have demonstrated that it is safe and efficacious for MDD in doses up to 20 mg/day. Additionally, there is evidence that vortioxetine improves cognitive function in adults with MDD, and the improvement in cognitive function appears to be independent of improvement of depression symptoms.

Recommendation

Consider the addition of vortioxetine to the drug formulary on regular status as it provides another SSRI treatment option for patients who may not have a clinical response to other offered antidepressants. Additionally, it may be beneficial for patients who have deficits in cognitive functioning with MDD.

References

1. Trintellix (vortioxetine) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals America Inc; September 2023. label (fda.gov)
2. Lexicomp Online, Vortioxetine (TRINTELLIX). Waltham, MA: UpToDate, Inc.; September 9, 2023. https://online.lexi.com.
3. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*. 2014;17(10):1557-1567.

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