Vortioxetine (Brintellix®)

National Drug Monograph
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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Vortioxetine is a serotonin reuptake inhibitor, 5-HT_3 receptor antagonist and 5-HT_{1A} receptor agonist.
- FDA labeled indication: Major depressive disorder (MDD).
- Pharmacokinetics: Primarily metabolized via CYP2D6.
- Dose: Oral:
    - Start at 10mg once daily for seven days, then increase to 20mg/day as tolerated (titrated up after one week in clinical trials). Consider a 5mg/day starting dose for patients who do not tolerate higher doses. Maximum dose: 20 mg/day.
- Vortioxetine can be taken with or without food.
- The maximum recommended dose in known CYP2D6 poor metabolizers is 10mg/day.
- Vortioxetine has demonstrated efficacy superior to placebo in patients with major depressive disorder.
- Adverse drug events:
  The most frequent adverse effects reported during clinical trials were nausea, diarrhea and headache. However, other adverse effects similar to those caused by other serotonergic antidepressants may occur.
- Vortioxetine can be discontinued abruptly. However, it is recommended that doses of 15-20mg/day be reduced to 10mg/day for one week prior to full discontinuation if possible to minimize the likelihood of discontinuation withdrawal symptoms.
- Vortioxetine carries many of the same warning and precautions as other antidepressants, including risk for serotonin syndrome, abnormal bleeding, activation of mania/hypomania and SIADH.
- Drug interactions:
    - Interactions involving the cytochrome P450 system, in particular CYP2D6, may affect vortioxetine concentrations. Vortioxetine is highly bound to plasma proteins, and may thereby interact with other highly protein-bound drugs.
    - Concurrent use of vortioxetine with monoamine oxidase inhibitors, linezolid or IV methylene blue is contraindicated
- Based on the available data, vortioxetine is effective but does not offer significant advantages over other currently available medications for the treatment of major depressive disorder. Vortioxetine is available in 5mg, 10mg and 20mg tablets.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating vortioxetine for possible addition to the VA National Formulary; (2) to define the role of vortioxetine in therapy for major depressive disorder; and (3) to identify parameters for the rational use of vortioxetine in the VA.

Pharmacology/Pharmacokinetics[1]

Mechanism of action:

The mechanism of the antidepressant effect of vortioxetine is not fully understood, but is thought to be related to inhibition of the reuptake of serotonin (5-HT) in the central nervous system (CNS). It also has several other activities including 5-HT_3 receptor antagonism and 5-HT_{1A} receptor agonism. The contribution of these activities to vortioxetine's antidepressant effect has not been established.

Pharmacokinetics:

Vortioxetine pharmacological activity is due to the parent drug. The pharmacokinetics of vortioxetine are linear and dose-proportional when vortioxetine is administered at a dose of 2.5-60mg once daily. The mean terminal half-life is approximately 66 hours, and steady-state plasma concentrations are typically achieved within two weeks of dosing.

Table 1 Comparative Pharmacokinetics of Vortioxetine

Parameter	Vortioxetine	Sertraline	Citalopram
Metabolism	Hepatic via CYP 2D6 to inactive metabolite (primary)	Hepatic via N-demethylation (primary)	Hepatic via CYP3A4 and CYP2C19; N-demethylation (primary)
Elimination	59% urine (as metabolites); 26% feces (as metabolites)	Urine (40-45%) and feces (40-45%); 12-14% unchanged	Urine (20%); 12-13% unchanged
Half-life	~66 hours	~24 hours	~35 hours
Protein binding	98%	99%	80%
Bioavailability	75%; no effect of food	100%	80%

FDA Approved Indication(s)

- Treatment of major depressive disorder (MDD)

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Other antidepressant medications are FDA approved and/or used off-label to treat anxiety disorders, bipolar depression, post-traumatic stress disorder (PTSD) and chronic pain. A PubMed search found that vortioxetine has also been investigated for treatment of generalized anxiety disorder and treatment of cognitive dysfunction.

Current VA National Formulary Alternatives

Other antidepressants on the VA National Formulary include SSRIs (citalopram, fluoxetine, sertraline, paroxetine); tricyclic antidepressants (TCAs); venlafaxine; bupropion; mirtazapine; trazodone; and monoamine oxidase inhibitors (MAOIs). Of these options, only MAOIs are restricted to mental health providers with criteria for use.

Dosage and Administration[1]

The recommended starting dose of vortioxetine is 10 mg administered orally once daily without regard to meals. The dose should then be increased to 20 mg/day as tolerated (titrated up after one week in clinical trials). Consider reducing dose to 5 mg/day for patients who do not tolerate higher doses. The maximum recommended daily dose is 20mg.

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.

Dose adjustment in renal impairment

No dose adjustment is necessary based on renal function (from mild renal impairment to end-stage renal disease).

Dose adjustment in hepatic impairment

No dose adjustment is necessary for mild or moderate hepatic impairment.
Vortioxetine has not been studied in patients with severe hepatic impairment, and is therefore not recommended for use in patients with severe hepatic impairment.

Dose adjustment in the elderly

No dose adjustment is recommended on the basis of age.

Dose adjustment in CYP2D6 poor metabolizers

The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers.

Efficacy Measures

CGI – Clinical Global Impression

Three-item scale that asks the clinician to rate the patient:

- Severity of Mental Illness (CGI-S): scored 1-7, with higher scores indicating greater illness. Score of 0 = not assessed.
- Global improvement (CGI-I): scored 1-7, with lower scores indicating improvement and higher scores indicating worsened condition. Score of 0 = not assessed.
- Efficacy index: Considers therapeutic effect and side effects of antidepressant medication to yield a score ranging from 1-16.

HAM-A – Hamilton Anxiety Rating Scale

14-item clinician-rated scale to assess severity of anxiety; score range 0-56, with higher scores indicating more anxiety

- <17 = mild severity
- 18-24 = mild to moderate severity
- 25-30 = moderate to severe
- ≥30 = severe anxiety

HAM-D_{17} (HDRS-17) and HAM-D_{24} (HDRS-24) – Hamilton Depression Rating Scale, 17- and 24-item

Multi-item clinician-administered scales used to rate the severity of adult depression; addresses mood, feelings of guilt, suicidal ideation, insomnia, agitation or retardation, anxiety, weight loss and somatic symptoms.

- 0-7 = normal/symptoms absent
- 8-13 = mild depression
- 14-18 = moderate depression
- 19-22 = severe depression
- ≥23 = very severe depression
- "Response" = reduction in HAM-D score by ≥50% from baseline
- "Remission" = HAM-D17 score ≤7

MADRS – Montgomery-Asberg Depression Rating Scale

Ten-item clinician-administered scale used to measure the severity of depressive symptoms. Includes items related to apparent and reported sadness, inner tension, reduced sleep or appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts.

- 0-6 = normal/symptoms absent
- 7-19 = mild depression
- 20-34 = moderate depression
- >34 = severe depression
- "Response" = reduction in MADRS score by ≥50% from baseline
- "Remission" = MADRS score ≤10

Sheehan Disability Scale

Self-administered questionnaire that includes three 10-point visual analog scales; produces a global functional impairment score that ranges from 0 (unimpaired) to 30 (highly impaired).

Summary of efficacy trials

Several short-term and long-term randomized controlled trials have been conducted to assess the efficacy, safety and tolerability of vortioxetine. Efficacy results are mixed. Several trials have shown vortioxetine to be statistically superior to placebo and/or comparable in efficacy to existing approved therapies (active reference studies). However, two trials have shown a therapeutic benefit over placebo only at higher doses, and four others have shown no significant benefit of vortioxetine over placebo. Existing data from randomized controlled trials are discussed below.

Short-term efficacy trials

Henigsberg et al (2012)[2]

Study Design

- This 8-week randomized double-blind placebo-controlled multi-center trial examined the efficacy and tolerability of vortioxetine.
- 560 adult patients with MDD were randomized 1:1:1:1 to receive vortioxetine 1mg/day, 5mg/day, 10mg/day or placebo.
- Inclusion criteria:
    - patients aged 18-75yo
    - diagnosis of major depressive disorder (per DSM-IV criteria)
    - MADRS total score >26 (moderate to severe depression)
- Exclusion criteria:
    - Patients at risk for suicide per investigator judgment
    - Suicide attempt within past six months
    - Prior failure of two or more antidepressants (6 week trial or more)
    - History of psychiatric, neurologic or substance abuse disorder other than MDD
    - Current clinically significant medical illness
    - Significant abnormalities in vital signs or laboratory values
- Primary efficacy endpoint: change from baseline in HDRS-24 at Week 8
- Secondary efficacy endpoints:
    - Change from baseline in Sheehan Disability Scale (SDS)
    - Clinical Global Impression Scale-Global Improvement (CGI-I)
    - HDRS response rate (≥50% decrease in HDRS-24 from baseline)
    - HDRS remission rate (HDRS-17 total score ≤7)
    - HDRS-24 score in patients with baseline HAM-A ≥20 (moderate-severe anxiety)
    - MADRS response rate (≥50% decrease in MADRS score from baseline)
    - MADRS remission rate (MADRS total score ≤10)
    - MADRS total score

Baseline Patient Characteristics

- Mean age 46 years; 63% female; 86% Caucasian/11% Asian/2% Black.
- The mean baseline HDRS-24 score was 32.6; mean baseline MADRS score 30.8.
- No information provided about previous treatment or history of major depressive episodes.

Results

Table 2: Change in primary and secondary efficacy endpoints from baseline at Week 8 (full analysis set)

Endpoint	Placebo	Vortioxetine 1mg	Vortioxetine 5mg	Vortioxetine 10mg
Primary Endpoint				
HDRS-24 total score (MMRM)				
Total treatment group n	128	124	129	122
LS mean change from baseline (SE)	-11.30 (0.738)	-14.82 (0.745)	-15.42 (0.743)	-16.23 (0.755)
LS mean difference from placebo (SE)		-3.52 (1.04)	-4.12 (1.04)	-4.93 (1.05)
P value		<0.001	<0.001	<0.001
95% CI		(-5.57 to -1.47)	(-6.17 to -2.08)	(-6.99 to -2.86)
Standardized effect size		0.37	0.41	0.54
Secondary Endpoints				
MADRS total score (MMRM)				
Total treatment group n	128	124	129	122
LS mean change from baseline (SE)	-10.91 (0.708)	-14.89 (0.715)	-15.09 (0.712)	-15.65 (0.728)
LS mean difference from placebo (SE)		-3.99 (1.00)	-4.18 (1.00)	-4.75 (1.01)
P value		<0.001	<0.001	<0.001
95% CI		(-5.95 to -2.02)	(-6.14 to -2.22)	(-6.74 to -2.76)
Standardized effect size		0.44	0.50	0.58
SDS (MMRM)				
Total treatment group n	94	90	97	83
LS mean change from baseline (SE)	-6.54 (0.716)	-6.58 (0.729)	-7.65 (0.713)	-8.08 (0.756)
LS mean difference from placebo (SE)		-0.05 (1.01)	-1.11 (1.00)	-1.54 (1.03)
P value		0.963	0.263	0.135
95% CI		(-2.03 to 1.94)	(-3.07 to 0.84)	(-3.56 to 0.48)
Standardized effect size		0.01	0.15	0.24
CGI-I (MMRM)				
Total treatment group n	128	124	129	122
LS mean change from baseline (SE)	2.84 (0.089)	2.37 (0.090)	2.37 (0.089)	2.29 (0.091)
LS mean difference from placebo (SE)		-0.47 (0.13)	-0.47 (0.13)	-0.55 (0.13)
P value		<0.001	<0.001	<0.001
95% CI		(-0.72 to -0.23)	(-0.71 to -0.22)	(-0.80 to -0.30)
Standardized effect size		0.40	0.42	0.46
HDRS-24 total with HAM-A ≥20 (MMRM)				
Total treatment group n	62	65	57	65
LS mean change from baseline (SE)	-11.02 (1.017)	-15.16 (0.991)	-15.50 (1.063)	-15.61 (0.984)
LS mean difference from placebo (SE)		-4.13 (1.40)	-4.47 (1.45)	-4.59 (1.40)
P value		0.004	0.002	0.001
95% CI		(-6.90 to -1.37)	(-7.32 to -1.62)	(-7.34 to -1.84)
Standardized effect size		0.40	0.48	0.49
HDRS-24 response rate (LOCF)				
Total treatment group n	139	139	139	139
n (%)	32 (23.0)	66 (47.5)	63 (45.3)	69 (49.6)
P value		<0.001	<0.001	<0.001
Odds ratio vs. placebo		3.02	2.74	3.35
95% CI		(1.799 to 5.063)	(1.631 to 4.598)	(1.995 to 5.618)
HDRS-17 remission rate (LOCF)				
Total treatment group n	139	139	139	139
n (%)	16 (11.5)	29 (20.9)	34 (24.5)	33 (23.7)
P value		0.44	0.008	0.007
Odds ratio vs. placebo		1.982	2.425	2.447
95% CI		(1.019 to 3.855)	(1.264 to 4.653)	(1.273 to 4.706)
MADRS remission (LOCF)				
Total treatment group n	139	139	139	139
n (%)	23 (16.5)	36 (25.9)	40 (28.8)	37 (26.6)
P value		0.062	0.015	0.026
Odds ratio vs. placebo		1.75	2.06	1.95
95% CI		(0.97 to 3.16)	(1.15 to 3.67)	(1.08 to 3.52)
MADRS response (LOCF)				
Total treatment group n	139	139	139	139
n (%)	34 (24.5)	65 (46.8)	61 (43.9)	68 (48.9)
P value		<0.001	<0.001	<0.001
Odds ratio vs. placebo		2.717	2.414	2.929
95% CI		(1.631 to 4.527)	(1.447 to 4.027)	(1.752 to 4.885)

HAM-A = Hamilton Rating Scale for Anxiety; HDRS-17 = 17-Item Hamilton Depression Rating Scale; HDRS-24 = 24-Items Hamilton Depression Rating Scale; LOCF = last observation carried forward; MADRS = Montgomery-Asberg Depression Rating Scale; MMRM = mixed model for repeated measurements.

There was a statistically significant reduction from baseline in HDRS-24 at Week 8 for vortioxetine 10mg vs. placebo, with separation beginning at Week 2. Significant improvements were seen (P <0.05) in HDRS-24 total score, response and remission rates, CGI-I score, MADRS total score, and HDRS-24 total score in subjects with baseline HAM-A ≥20 at Week 8 for all vortioxetine doses compared with placebo. No significant differences were seen in SDS scores between vortioxetine and placebo. The authors conclude that all doses were well-tolerated and that vortioxetine 10mg was effective for treatment of MDD.

Limitations

- Results may not be generalizable to the veteran population: the patients studied were relatively young, nearly two-thirds were female, and those with medical/psychiatric comorbidities were excluded.

Boulenger et al (2013)[3]

Study Design

This 8-week double-blind randomized placebo-controlled active-reference multi-center trial assessed the safety and efficacy of vortioxetine at doses of 15mg and 20mg daily (upper end of approved dosing range). A group of 608 adult patients were randomized 1:1:1:1 to receive vortioxetine 15mg/day, vortioxetine 20mg/day, placebo, or the active reference medication duloxetine 60mg/day. Patients receiving vortioxetine were initiated at 10mg/day for one week before increasing to the target dose. Inclusion and exclusion criteria were similar to those selected by Henigsberg et al.

- Primary efficacy endpoint: change from baseline in MADRS total score at week 8 (mixed model for repeated measurements).
- Key secondary endpoints: MADRS responders; CGI-I score; MADRS total score in patients with baseline HAM-A ≥20 (significant anxiety symptoms); remission (MADRS ≤10) and Sheehan Disability Scale total score at week 8.

Baseline Patient Characteristics

- Mean age 47 years (range 18-74 years); 66% female; 98% Caucasian.
- The mean baseline MADRS total score was 31.4±3.5 and mean CGI-S score was 4.8, indicating moderate-to-severe depression.
- Patients had a mean number of two previous major depressive episodes and a median duration of 22 weeks (range 14–317 weeks) for the current episode.
- There were no clinically relevant differences between groups at baseline.

Results

Table 3: Change in primary and secondary efficacy endpoints from baseline at week 8

	Placebo n=158	**Vortioxetine 15mg** n=151		**Vortioxetine 20mg** n=151		**Duloxetine 60mg** n=147	
	Δ baseline	**Δ baseline**	**p-value**	**Δ baseline**	**p-value**	**Δ baseline**	**p-value**
Δ MADRS total score	-11.7	-17.2	<0.0001	-18.8	<0.0001	-21.2	<0.0001
MADRS response	32.3%	57.0%	<0.0001	61.6%	<0.0001	74.0%	<0.0001
CGI-I score	2.86	2.18	<0.0001	1.92	<0.0001	1.75	<0.0001
Δ MADRS (HAM-A ≥20)	-12.2	-17.4	0.0007	-18.6	<0.0001	-20.9	<0.0001
MADRS remission	19.0%	34.9%	0.0016	38.4%	0.0002	54.1	<0.0001
Δ SDS total score	-4.5	-7.7	0.0054	-8.4	0.0005	-11.4	<0.0001

Both doses of vortioxetine outperformed placebo in all the predefined key secondary efficacy analyses, including response and remission based on the MADRS. Separation from placebo was seen from week 2 onwards (vortioxetine 20mg) and week 4 onwards (vortioxetine 15 mg). Vortioxetine showed an effect on anxiety symptoms over placebo, as demonstrated by a decrease of HAM-A total scores of 9.6 (15mg) and 11.1 (20mg) throughout the 8-week treatment period. The authors conclude that both doses of vortioxetine were effective and well-tolerated, with nausea and headaches being the most common adverse effects.

Limitations

- 98% of patients in this study were Caucasian; it is unclear whether differences in efficacy and safety/tolerability would be seen in patients from other racial backgrounds.
- Results may not be generalizable to the veteran population: the patients studied were relatively young, nearly two-thirds were female, and those with medical/psychiatric comorbidities were excluded.

Long-term efficacy trials

Baldwin et al (2012)[4]

Study Design

A total of 535 patients entered this 52-week, open-label extension study after completing an 8-week lead-in study during which they received vortioxetine 2.5mg/day, 5mg/day, 10mg/day, duloxetine 60mg/day, or placebo.[5] In that initial study, large reductions in mean MADRS score from baseline were seen in all groups. However, the trial was considered to be failed because neither vortioxetine nor the active reference duloxetine significantly outperformed placebo.

All patients in the extension study received 5 mg/day of vortioxetine for the first week. Thereafter, the dosage was flexible (2.5, 5, or 10 mg/day), and could be increased, maintained, or decreased at scheduled study visits per the investigator's judgment.

Baseline Patient Characteristics

- Mean age 46 years (range 19–76 years); 68.4% female, 81.5% Caucasian, 17.6% Asian.
- Between 68% and 70% of the patients in each treatment group had experienced a previous major depressive episode. The current episode had typically started about 9 months prior to enrollment in the 8-week lead-in study.[5]
- Patients entered the extension phase of this study with a mean MADRS total score of 13.5±8.7 (decreased from baseline MADRS score 31.9±4.3 at the beginning of the 8-week lead-in trial[5]).

Results

At week 52, the mean MADRS total score had decreased to 5.5 ± 6.0. By the end of the study, the proportion of responders had increased from 63% (after 8-week lead-in) to 94%. The proportion of patients in remission (MADRS ≤10) increased from 42% (after 8-week lead-in) to 83%. Patients who were in remission at the start of the study had a relapse rate (MADRS ≥22) of 9.7% during the 52-week study period.

Table 4: Patients achieving response and remission during a 52-week extension study

Visit Week	Total number of patients	MADRS total score (mean±SD)	*Response (n, %)	**Remission (n, %)
0	535	13.5±8.7	336 (62.8)	226 (42.2)
4	512	10.9±7.7	392 (76.6)	280 (54.7)
8	466	9.2±7.3	385 (82.6)	306 (65.7)
24	387	6.6±5.8	358 (92.5)	303 (78.3)
52	329	5.5±6.0	310 (94.2)	273 (83.0)

Limitations

- Of note, only 61% of patients enrolled completed the study; it is therefore possible that total response and remission rates were actually lower than stated. The authors point out that this percentage is similar to those seen in other long-term antidepressant studies (citing a 58% completion rate in a similar study of duloxetine and 74% with escitalopram).
- This study was not placebo-controlled by design, so the inability to draw conclusions about the causality of improvement in depressive symptoms is limited. However, the authors do conclude that vortioxetine was effective and well-tolerated at the doses studied, and that therapeutic effect was maintained over one year.

Boulenger et al (2013)[6]

Study Design

This study was designed to assess the effect of vortioxetine on prevention of relapse of major depressive disorder. The study design consisted of two consecutive periods. The first period was a 12-week, open-label, flexible-dose treatment period in which 639 patients were treated with vortioxetine 5-10mg/day. Patients who reached remission (MADRS total score ≤10) at weeks 10 and 12 were randomized to either vortioxetine (continued at their previous dose fixed at week 8) or placebo for a period of 24-64 weeks.

- Primary endpoint: time to relapse. Relapse was defined as a MADRS total score ≥22 or an insufficient therapeutic response, as judged by the investigator.

Patients included in this study were aged 18–75 years and had a primary diagnosis of MDD with current major depressive episode of 4 weeks or more, at least one prior major depressive episode, and a baseline MADRS total score ≥26.

Exclusion criteria were similar to those used by Henigsberg et al, except that this study specified a broader range of medications that patients could not be taking during the study period:

- investigational drugs
- narcotic analgesics
- anorexics,
- anticonvulsants
- antidepressants
- psychoactive herbal remedies
- antidiarrheal agents
- antihistamines
- antimigraine agents
- antiemetics
- antiobesity agents
- antipsychotics
- anxiolytics (including benzodiazepines)
- cough or cold agents
- diuretics
- systemic steroids
- mood stabilizers
- sedatives or hypnotics
- episodic insulin, hypoglycemic agents or hormones

Baseline Patient Characteristics

- Two thirds female; 78% Caucasian and 19% Asian. The average age was 45 years (range 18-75 years).
- The mean length of the current major depressive episode was about 23 weeks (range 4 weeks-4 years), and the mean number of major depressive episodes was 2.1.
- There were no significant differences between patients treated with vortioxetine or placebo at randomization.

Results

Of the 639 patients initiated on vortioxetine in this study, 400 reached remission at week 8 and were randomized to vortioxetine or placebo in the extension phase.

Time to relapse: the primary analysis of time to relapse (full-analysis set, Cox proportional hazard model) showed a statistically significant difference in favor of vortioxetine versus placebo at 24 weeks into the second phase (hazard ratio 2.01; 95% confidence interval: 1.26–3.21; p=0.0035). Proportion of relapse: The proportion of patients who relapsed was 13% in the vortioxetine group (n=27) and 26% in the placebo group (n=50); p=0.0013.

Covariate analysis showed no statistically significant effect on the primary efficacy analysis of time to relapse (within first 24 weeks of double-blind period) of baseline MADRS score, sex, study center/country or weight. Interestingly, there was a statistically significant (*p*=0.016) interaction between treatment and Asian race. There was a greater effect of treatment and a lower risk of relapse for Caucasian patients than for Asian patients.

The authors conclude that vortioxetine was effective in preventing relapse of MDD and was well tolerated as maintenance treatment.

Limitations

- Extensive exclusion criteria may limit the generalizability of results to real-world-patients.
- Relapse was defined by MADRS score, as opposed to DSM-IV criteria for MDD.

Table 5: Summary of negative or failed trials[7]

Study	Length (weeks)	n randomized	Vortioxetine dose (n)	Active control and dose (n)	n Placebo	Comments
Baldwin et al.[5]	8	776	2.5mg/day (255), 5mg/day (159), 10mg/day (153)	Duloxetine 60mg/day (157)	152	Failed trial; none of the active treatment groups (including duloxetine) were superior to placebo on MADRS (primary endpoint) using LOCF 79% completion rate.
Mahableshwarkar et al.[8]	8	611	2.5mg/day (153), 5mg/day (153)	Duloxetine 60mg/day (152)	153	Negative trial; vortioxetine not statistically superior on primary efficacy endpoint (improvement in HDRS-24 score) vs. placebo using LOCF; duloxetine was superior to placebo. 74% completion rate.
Mahableshwarkar et al.[9]	8	469	10mg/day (157), 15mg/day (152)	None	160	Negative or failed trial. Vortioxetine not statistically superior on primary endpoint (MADRS) vs. placebo using MMRM; cannot determine negative vs. failed trial due to lack of active control. 82% completion rate.
Jain et. al[10]	6	600	5mg/day (300)	None	300	Negative or failed trial. Vortioxetine not statistically superior on primary endpoint (improvement in HDRS-24) vs. placebo using LOCF; cannot determine negative vs. failed trial due to lack of active control. 80% completion rate.

Adverse Events (AE) and Safety Data

Common Adverse Reactions in Placebo-Controlled Studies[1]

The most commonly observed adverse reactions in patients with major depressive disorder treated with vortioxetine in 6-8 week placebo-controlled studies were nausea, constipation and vomiting (common defined as incidence ≥5% and at least twice the rate of placebo).

Table 6 shows the incidence of common adverse reactions that occurred in ≥2% of patients treated for major depressive disorder with vortioxetine (any dose) and at least 2% more frequently than in placebo-treated patients in the 6 to 8 week placebo-controlled studies.

Table 6: Common adverse reactions occurring in ≥2% of patients treated with vortioxetine and at least 2% greater than the incidence in patients treated with placebo

System Organ Class Preferred Term	Vortioxetine 5mg/day	Vortioxetine 10mg/day	Vortioxetine 15mg/day	Vortioxetine 20mg/day	Placebo
	N=1013 (%)	N=699 (%)	N = 449 (%)	N = 455 (%)	N = 1621 (%)
Gastrointestinal disorders					
Nausea	21	26	32	32	9
Diarrhea	7	7	10	7	6
Dry Mouth	7	7	6	8	6
Constipation	3	5	6	6	3
Vomiting	3	5	6	6	1
Flatulence	1	3	2	1	1
Nervous system disorders					
Dizziness	6	6	8	9	6
Psychiatric disorders					
Abnormal dreams	<1	<1	2	3	1
Skin and subcutaneous tissue disorders					
Pruritus	1	2	3	3	1

Sexual dysfunction in placebo-controlled studies[1]

The Arizona Sexual Experiences Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in seven placebo-controlled trials. The ASEX scale includes five questions that pertain to sex drive, ease of arousal, ability to achieve erection (men) or lubrication (women), ease of reaching orgasm, and orgasm satisfaction. Results suggest a dose-dependent increase in sexual dysfunction with vortioxetine.

Table 7 ASEX Incidence of treatment-emergent sexual dysfunction

	Vortioxetine 5mg/day N=65:67*	Vortioxetine 10mg/day N=94:86*	Vortioxetine 15mg/day N=57:67*	Vortioxetine 20mg/day N=67:59	Placebo N=135:162
Treatment-emergent sexual dysfunction, females	22%	23%	33%	34%	20%
Treatment-emergent sexual dysfunction, males	16%	20%	19%	29%	14%

*Sample size for each dose group is the number of patients (females: males) without sexual dysfunction at baseline.

Deaths and Other Serious Adverse Events

Boulenger and colleagues reported serious adverse effects in five patients (0.82%): two patients in the vortioxetine 20mg group and three patients in the duloxetine group. One vortioxetine 20mg patient and one duloxetine patient had serious AEs related to suicidal behavior and self-harm. Frequency of suicidal ideation was reported as follows: 11.4% (placebo), 9.9% (vortioxetine 15mg), 9.3% (vortioxetine 20mg) and 6.1% (duloxetine).

Henigsberg and colleagues[2] reported that 6 (1.1%) subjects experienced a serious adverse effect during an 8-week study. The incidence was similar across treatment groups: pancreatitis and suicide attempt in the vortioxetine 10mg/day group, tachycardia in the vortioxetine 5mg/day group, hypertensive crisis in the vortioxetine 1mg/day group, and severe dizziness and

pancreatitis in patients taking placebo. Only the pancreatitis in the vortioxetine 10mg group was deemed potentially related to treatment. No deaths occurred during this study.

In the open-label 52-week extension study, Baldwin and colleagues[4] reported two deaths (one motorcycle accident and one fall from a balcony prior to beginning study medication). Neither death was deemed related to depression or adverse effects of medication. Five patients had serious AEs related to suicidal behavior or self-harm. All were withdrawn from the study, and all recovered from the events. Four patients had serious AEs related to worsening of depression. The authors noted no new safety findings with long-term use.

In the relapse prevention study, Boulenger and colleagues reported serious AEs in four patients in the placebo group and seven patients in the vortioxetine group. One patient died due to pancreatic cancer approximately eight months after the last dose of open-label treatment. Two patients died during the screening period, both by suicide.

Tolerability

Adverse Reactions Reported as Reasons for Discontinuation of Treatment[1]

In pooled 6 to 8 week placebo-controlled studies, the incidence of patients who discontinued treatment with vortioxetine or placebo due to adverse reactions was as follows:

Table 8: Pooled discontinuation rate of vortioxetine or placebo due to adverse effects in 6-8 week studies

Medication and dose	Discontinuation rate
Vortioxetine 5mg/day	5%
Vortioxetine 10mg/day	6%
Vortioxetine 15mg/day	8%
Vortioxetine 20mg/day	8%
Placebo	4%

Nausea was the most common adverse effect leading to discontinuation.

Contraindications[1]

- Hypersensitivity to vortioxetine or any components of the vortioxetine product formulation
- Monoamine Oxidase Inhibitors (MAOIs):
  - Do not use MAOIs intended to treat psychiatric disorders with vortioxetine or within 21 days of stopping treatment with vortioxetine.
  - Do not use vortioxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders.
- Do not start vortioxetine in a patient who is being treated with linezolid or intravenous methylene blue.

Warnings and Precautions[1]

- **Serotonin syndrome** has been reported with serotonergic antidepressants (SSRIs, SNRIs, and others), including with vortioxetine, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort).
  - If symptoms of serotonin syndrome 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.
- **Abnormal bleeding**: 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 co-administered with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation.
- **Activation of mania/hypomania** can occur with antidepressant treatment. Screen patients for bipolar disorder (5.4).

- **Hyponatremia** can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Special Populations[1]
Pregnancy: Pregnancy Category C

Risk Summary
There are no adequate and well-controlled studies of vortioxetine in pregnant women. Vortioxetine caused developmental delays when administered during pregnancy to rats and rabbits at doses 15 and 10 times the maximum recommended human dose (MRHD) of 20 mg, respectively. Developmental delays were also seen after birth in rats at doses 20 times the MRHD of vortioxetine given during pregnancy and through lactation. There were no teratogenic effects in rats or rabbits at doses up to 77 and 58 times the MRHD of vortioxetine, respectively, given during organogenesis. The incidence of malformations in human pregnancies has not been established for vortioxetine. Vortioxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations
Neonates exposed to SSRIs or SNRIs during pregnancy have developed complications requiring prolonged hospitalization, respiratory support and tube feeding. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, constant crying and pulmonary hypertension. When treating a pregnant woman with vortioxetine during the third trimester, the provider should carefully consider the potential risks and benefits of treatment.

Nursing Mothers
It is not known whether vortioxetine is present in human milk. Vortioxetine is present in the milk of lactating rats.

Pediatric Use
Clinical studies on the use of vortioxetine in pediatric patients have not been conducted; therefore, the safety and effectiveness of vortioxetine in the pediatric population have not been established.

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 (24-45 years old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

Patients age 65 and older are represented in clinical trials of vortioxetine. One 8-week study has specifically evaluated vortioxetine in elderly patients with recurrent major depressive disorder. This study found vortioxetine to be safe and efficacious in the elderly (mean age 71 years) at a dose of 5mg/day.[11]

Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event.

Use in Other Patient Populations
No dose adjustment of vortioxetine on the basis of race, gender, ethnicity, or renal function (from mild renal impairment to end-stage renal disease) is necessary. In addition, the same dose can be administered in patients with mild to moderate hepatic impairment. Vortioxetine has not been studied in patients with severe hepatic impairment. Therefore, vortioxetine is not recommended in patients with severe hepatic impairment.

Sentinel Events
No data available.

Look-alike / Sound-alike (LA / SA) Error Risk Potential
As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

LA/SA for generic name ***vortioxetine****: atomoxetine, fluoxetine, duloxetine, reboxitine, voriconazole*

LA/SA for trade name **Brintellix®**: *Brisdelle, Brintenal, Brilinta*

Drug Interactions
Drug-Drug Interactions[1]
- Strong inhibitors of CYP2D6: Reduce vortioxetine dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) is co-administered.
- Strong CYP Inducers: Consider increasing vortioxetine dose when a strong CYP inducer (e.g., rifampin, carbamazepine, or phenytoin) is co-administered for more than 14 days. The maximum recommended dose should not exceed 3 times the original dose.

A study conducted by Chen et al evaluated the following potential drug interactions for vortioxetine.[12] The authors concluded that dosage adjustment may be required when vortioxetine is co-administered with bupropion or rifampicin.

Table 9: Pharmacokinetic interactions between vortioxetine and other drugs

Drug	Proposed mechanism of interaction with vortioxetine	Results
Bupropion	CYP2D6 inhibitor and CYP2B6 substrate	18% increase in Cmax of bupropion; no effect on AUC of bupropion. 114% increase in Cmax of vortioxetine; 128% increase in AUC of vortioxetine.
Fluconazole	CYP2C9, CYP2C19 and CYP3A inhibitor	15% increase in Cmax of vortioxetine; 46% increase in AUC of vortioxetine.
Ketoconazole	CYP3A and P-glycoprotein Inhibitor	26% increase in Cmax of vortioxetine; 30% increase in AUC of vortioxetine.
Rifampicin	CYP inducer	51% decrease in Cmax of vortioxetine; 72% decrease in AUC of vortioxetine.
Ethinyl estradiol/ levonorgestrel	CYP 3A substrates	No clinically significant effect on AUC or Cmax of ethinyl estradiol/levonorgestrel.
Omeprazole	CYP2C19 substrate/inhibitor	No clinically significant effect on AUC or Cmax of vortioxetine.

Acquisition Costs
Refer to VA pricing sources for updated information.

Pharmacoeconomic Analysis
No published pharmacoeconomic evaluations found.

Conclusions
The available evidence suggests that vortioxetine is a well-tolerated and likely effective medication for the treatment of major depressive disorder. However, its anticipated role in therapy is limited at this time due to its high cost and similar effectiveness relative to other safe and well-tolerated antidepressant medications on the VA formulary. Trials that have included an

active reference medication have used SNRIs, and no published data comparing vortioxetine to first-line SSRI therapy is available. Vortioxetine may prove to be a useful option for patients who have failed adequate trials of formulary antidepressants.

Vortioxetine is not currently FDA-approved for the treatment of generalized anxiety disorder, but several trials have demonstrated positive results when used for this indication. Future research may provide additional support for approval of vortioxetine for generalized anxiety disorder, which would add to its utility and potentially support its use in patients with concurrent depression and anxiety.

Based on the results of placebo-controlled clinical trials, vortioxetine does not appear to offer advantages in safety or efficacy to other antidepressants on the VANF. Therefore, use of vortioxetine should be limited to Veterans with MDD already being treated with vortioxetine who have demonstrated a satisfactory therapeutic response or remission.

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Addendum (November 2015)

Two meta-analyses and systematic reviews on the efficacy of vortioxetine have been published since the PBM monograph was completed. The first included 5 trials, 4 were included in the PBM monograph, the fifth trial compared vortioxetine 5 mg and 10 mg to placebo with venlafaxine as an active control. Vorioxetine was found to produce a significantly greater reduction in MADRS total score from baseline compared to placebo (WMD = -3.92; 95%CI -5.28, -2.581). This difference was greatest with higher doses of vortioxetine. The odds of treatment response (≥50% reduction in MADRS) was nearly 3-times greater with vortoxetine than placebo (OR=2.87; 2.39, 3.44). Patients assigned to vortioxetine were more likely to experience an adverse event than those assigned to placebo (OR = 1.21; 1.06, 1.38).

The second meta-analysis included 12 trials (7 were included in the PBM monograph). Compared to placebo, vortioxetine was more effective in reducing depression symptom scale scores (SMD = -0.217; -0313, -0122), i.e., a small effect size. Those assigned to vortioxetine were significantly more likely to achieve response and remission (OR = 1.652; 1.321, 2.067 and OR = 1.399; 1.104, 1.773). Analysis of the seven trials that included an active comparator (duloxetine, venlafaxine or agomelatine) found no difference in treatments (SMD = 0.081; -0.062, 0.223), nor did the odds of response or remission. Analysis of published trials found SNRIs/agomelatine to be superior to vortioxetine in response (OR = 0.719; 0.869) and remission (OR=0.672; 0.495, 0.912), yet there was no difference in these rates in unpublished trials.

Both meta-analysis found the rate of discontinuation due to adverse events to be significantly higher, 21% and 53%, respectively, with vortioxetine than placebo, but no higher than with comparison antidepressants.

As concluded in the original monograph, “Based on the results of placebo-controlled clinical trials, vortioxetine does not appear to offer advantages in safety or efficacy to other antidepressants on the VANF. Therefore, use of vortioxetine should be limited to Veterans with MDD already being treated with vortioxetine who have demonstrated a satisfactory therapeutic response or remission.”

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Prepared April 2014 by Kristen Wendell, Pharm.D. and William Florkowski, Pharm.D., BCPP;
Addendum prepared and added November 2015, Todd Semla, MS, Pharm.D,BCPS
Contact person: Todd Semla, MS, PharmD, BCPS