More than 2 million patients with MDD have been treated with TRINTELLIX since 2013[1,2]

INDICATION

TRINTELLIX is indicated for the treatment of Major Depressive Disorder (MDD) in adults.

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS & BEHAVIORS

- **Antidepressants increased the risk of suicidal thoughts and behaviors 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.**
- **TRINTELLIX is not approved for use in pediatric patients.**

Please see additional Important Safety Information throughout this brochure, and click for Full Prescribing Information.

TRINTELLIX MONOTHERAPY RELIEVED THE OVERALL SYMPTOMS OF MDD[1]

Based on 6 short-term clinical studies that[1]:

- Were randomized, placebo-controlled, and double-blind, and lasted 6 to 8 weeks
- Gave adult patients 5 to 20 mg of TRINTELLIX once daily or placebo
- Measured patients' improvement in the total score of MADRS or HAM-D_{24}
- Concluded that at least 1 of the studied doses of TRINTELLIX in each short-term clinical study was superior to placebo
- Found the most common adverse reactions (incidence ≥5% and at least twice the rate of placebo in 6- to 8-week studies) were nausea, constipation, and vomiting

Two additional US studies failed to show effectiveness at the 5-mg dose.

RELIEF AS EARLY AS WEEK 2[1]
In the short-term studies, patients experienced relief from symptoms as early as Week 2, and the full antidepressant effect by Week 4 or later.

HAM-D_{24}, Hamilton Depression 24-item Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS

- **Hypersensitivity:** Hypersensitivity to vortioxetine or any component of the TRINTELLIX formulation. Hypersensitivity reactions including anaphylaxis, angioedema, and urticaria have been reported in patients treated with TRINTELLIX.
- **Monoamine Oxidase Inhibitors (MAOIs):** Do not use MAOIs intended to treat psychiatric disorders with TRINTELLIX or within 21 days of stopping treatment with TRINTELLIX, due to an increased risk of serotonin syndrome. Do not use TRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders.

FDA-APPROVED FOR YOUR ELDERLY PATIENTS[1]

One of the 6 short-term studies[1]:

- Was a randomized, double-blind, placebo-controlled, fixed-dose study
- Lasted 8 weeks and included MDD patients aged 64-88 who received TRINTELLIX 5 mg or placebo*
- Showed significant improvement in overall MDD symptoms as measured by the mean change from baseline in HAM-D_{24} total score

Hyponatremia has occurred as a result of treatment with serotonergic drugs, including TRINTELLIX. Elderly patients may be at greater risk of developing hyponatremia with a serotonergic antidepressant.[1]

Please see Warning and Precaution for Hyponatremia listed in the Important Safety Information on page 10.

*Patients meeting diagnostic criteria for recurrent MDD had at least 1 previous major depressive episode before age 60 without any comorbid cognitive impairment.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS (cont'd)

- **Linezolid and Methylene Blue:** Do not start TRINTELLIX in a patient being treated with MAOIs such as linezolid or intravenous methylene blue, due to an increased risk of serotonin syndrome.

Please see additional Important Safety Information, including Boxed WARNING regarding Suicidal Thoughts and Behaviors, throughout this brochure, and click for Full Prescribing Information.

Trintellix
vortioxetine
5mg•10mg•20mg tablets

LONG-TERM RESULTS SEEN IN ADULTS AGED 18 TO 75 YEARS OLD[1,3]

TRINTELLIX significantly reduced the risk of recurrence* of depressive episodes in a US-based long-term study[1]

48-WEEK

randomized, double-blind, placebo-controlled, 2-phase study[1,3]

Patients who met remission criteria† after the 16-week, open-label phase with TRINTELLIX 10 mg/day were randomized in a double-blind phase 1:1:1:1 ratio to TRINTELLIX 5 mg/day, 10 mg/day, or 20 mg/day, or placebo for 32 weeks. About 52% of patients met the remission criteria for randomization.[1,3]

Risk of recurrence* was significantly greater with placebo (n=151)

VS

TRINTELLIX (n=429) during the first 28 weeks of the double-blind phase[1-3]

62% of patients taking TRINTELLIX were recurrence-free at Week 28 of the double-blind phase vs 46% on placebo[2‡]

*Recurrence of a depressive episode was defined as MADRS total score ≥22 or lack of efficacy as judged by the investigator.[1]
†Remission was defined as MADRS total score ≤12 at both Weeks 14 and 16.[1]
‡Percentage of patients with recurrence and percentage of patients recurrence-free at Week 28 were each divided by the total number of patients in the study.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

- **Suicidal Thoughts and Behaviors in Adolescents and Young Adults:** Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing TRINTELLIX, in patients whose depression is persistently worse, or who are experiencing emergence of suicidal thoughts and behaviors. In pooled analyses of placebo-controlled trials of antidepressants, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients ages 24 and younger was greater than in placebo-treated patients.

LONG-TERM STUDY SAFETY DATA FROM STUDY 10

ADVERSE EVENTS ≥5% IN THE OPEN-LABEL PERIOD[2]

ADVERSE EVENT	10 MG/DAY (n=1106)
Nausea	26.4%
Headache	8.2%
Dry mouth	5.2%
Nasopharyngitis	5.1%

- 6% of patients withdrew due to TEAEs[2]
- 9 SAEs occurred; only TRINTELLIX-related SAE was active suicidal ideation with a plan; 1 SAE was passive suicidal ideation[2]

ADVERSE EVENTS ≥5% IN AT LEAST 1 TRINTELLIX GROUP IN THE DOUBLE-BLIND PERIOD[2]

ADVERSE EVENT	PLACEBO (n=151)	5 MG/DAY (n=140)	10 MG/DAY (n=145)	20 MG/DAY (n=144)
Upper respiratory tract infection	4.0%	6.4%	6.2%	6.3%
Nasopharyngitis	2.6%	5.0%	4.8%	5.6%
Nausea	1.3%	2.9%	3.4%	9.0%
Weight increase	2.0%	3.6%	4.8%	5.6%
Back pain	1.3%	5.7%	0.0%	1.4%

- Discontinuations (due to TEAEs): 2.0%, 2.1%, 0.7%, and 4.9% for placebo, TRINTELLIX 5 mg/day, TRINTELLIX 10 mg/day, and TRINTELLIX 20 mg/day arms, respectively[2]
- 9 SAEs occurred; none deemed related to TRINTELLIX; 1 SAE was a completed suicide[2]

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

No significant effect on body weight in 6 short-term MDD studies and 1 (non-US) long-term MDD study[1]

No statistical analyses were conducted on weight change in the US-based long-term study; weight increase was a reported adverse reaction in the TRINTELLIX 20 mg group (≥5%).[2]

Some reports of weight gain have been received since product approval[1]

Please see additional Important Safety Information, including Boxed WARNING regarding Suicidal Thoughts and Behaviors, throughout this brochure, and click for Full Prescribing Information.

Trintellix vortioxetine 5mg·10mg·20mg tablets

SWITCHING TO TRINTELLIX IMPROVED SSRI-INDUCED SEXUAL DYSFUNCTION IN MDD PATIENTS[1]

Mean Change From Baseline in CSFQ-14 Total Score at Week 8 in a Head-to-Head Study[1,4]

Escitalopram 10 mg or 20 mg (n=207)		TRINTELLIX 10 mg or 20 mg (n=217)
+6.6	vs	+8.8

A randomized, double-blind, 8-week study compared TRINTELLIX with escitalopram on their effect on TESD induced by prior SSRI treatment.[1,4]

The most common AEs with an incidence of 5% or more for TRINTELLIX in this study were nausea, headache, dizziness, and generalized pruritus.[4]

Please see Warning and Precaution for Sexual Dysfunction listed in the Important Safety Information on page 10.

There was no loss in antidepressant effect after switching to TRINTELLIX or escitalopram[1]

Adult patients with MDD who were being effectively treated but experiencing SSRI-induced sexual dysfunction (from citalopram, paroxetine, or sertraline) switched to either TRINTELLIX or escitalopram.[1] Both groups started on 10 mg/day then increased to 20 mg/day at Week 1, followed by flexible dosing. Clinically meaningful improvement considered to be a 2- to 3-point increase in CSFQ-14 total score. The CSFQ-14 is a validated scale that measures sexual function, including the 3 phases of the sexual response cycle: desire, arousal, and orgasm.

AE, adverse event; CSFQ-14, Changes in Sexual Functioning Questionnaire; SSRI, selective serotonin reuptake inhibitor; TESD, treatment-emergent sexual dysfunction.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Serotonin Syndrome:** Serotonergic antidepressants, including TRINTELLIX, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, meperidine, methadone, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs.

SEXUAL DYSFUNCTION DATA AS REPORTED USING ASEX

Prospectively assessed incidence of adverse sexual reactions as reported using the ASEX in patients without sexual dysfunction at baseline in 7 placebo-controlled studies of TRINTELLIX 5 mg/day to 20 mg/day[1]*

	Placebo	TRINTELLIX 5 mg/day	TRINTELLIX 10 mg/day	TRINTELLIX 20 mg/day
Female patients	20% N=135	22% N=65	23% N=94	34% N=67
Male patients	14% N=162	16% N=67	20% N=86	29% N=59

Voluntary reports with TRINTELLIX were ≤5% (vs ≤2% with placebo) in 6- to 8-week placebo-controlled studies. Voluntarily reported adverse sexual reactions are known to be underreported.[1†]

*Incidence based on the number of subjects with sexual dysfunction during the study/number of subjects without sexual dysfunction at baseline (approximately 1/3 of the population across all study groups).[1] Sexual dysfunction was defined as a subject reporting any of the following on the ASEX scale at 2 consecutive visits during the study: a total score ≥19; any single item with a score ≥5; or 3 or more items that each had a score ≥4.

†Voluntarily reported adverse reactions related to sexual dysfunction were captured as individual event terms and aggregated to report overall incidence.[1]

ASEX, Arizona Sexual Experiences Scale.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Serotonin Syndrome (cont'd):** Serotonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Please see additional Important Safety Information, including Boxed WARNING regarding Suicidal Thoughts and Behaviors, throughout this brochure, and click for Full Prescribing Information.

Trintellix vortioxetine 5mg·10mg·20mg tablets

IMPROVED PATIENTS' SPEED OF PROCESSING, AN ASPECT OF COGNITIVE FUNCTION THAT MAY BE IMPAIRED IN MDD[1]

TRINTELLIX significantly improved speed of processing during the treatment of MDD in 2 studies, based on the number of correct responses on the DSST[1]*

STUDY 7

87% greater mean change vs placebo[1]

STUDY 8

58% greater mean change vs placebo[1]

Only TRINTELLIX has data on speed of processing during the treatment of MDD in its US Prescribing Information[5]

*In adults with acute MDD, TRINTELLIX improved performance on the DSST, a neuropsychological test that most specifically measures speed of processing, in two 8-week, randomized, double-blind, placebo-controlled studies (dosed once daily).[1] Speed of processing can be described as how quickly a person can accurately process information.[6]

The effects observed on the DSST may reflect improvement in depression. Comparative studies have not been conducted to demonstrate a therapeutic advantage over other antidepressants on the DSST.[1]

Safety data in Study 7

Common AEs (incidence ≥5% for TRINTELLIX) in Study 7 were nausea (16.4%, 20.8%, 4.1%) and headache (8.2%, 12.6%, 7.1%) for TRINTELLIX 10 mg/day, TRINTELLIX 20 mg/day, and placebo, respectively. SAEs were reported by 2 patients in the TRINTELLIX 20-mg group and 2 patients in the placebo group. Withdrawals due to TEAEs were 2.6% (TRINTELLIX 10 mg), 4.3% (TRINTELLIX 20 mg), and 4.1% (placebo).[7]

Safety data in Study 8

Common AEs (incidence ≥5% for TRINTELLIX) in Study 8 were nausea (20.4%, 4.2%), headache (10.2%, 8.4%), and diarrhea (5.6%, 2.6%) for TRINTELLIX and placebo, respectively. Withdrawals due to TEAEs were 3.6% (TRINTELLIX 10 mg/20 mg) and 3.7% (placebo). One patient in the TRINTELLIX group attempted suicide, and 1 patient in the placebo group was hospitalized for worsening of depression.[8]

DSST, Digit Symbol Substitution Test.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Serotonin Syndrome (cont'd):** Monitor all patients taking TRINTELLIX for the emergence of serotonin syndrome. Discontinue treatment with TRINTELLIX and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of TRINTELLIX with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

SAFETY OF TRINTELLIX WAS EVALUATED IN MORE THAN 5800 ADULT PATIENTS ACROSS MULTIPLE CLINICAL STUDIES[1]

Common adverse reactions occurring in ≥2% of patients treated with TRINTELLIX and at least 2% greater than the incidence in placebo-treated patients in 6- to 8-week studies[1]*

	PLACEBO (n=1621)	5 MG (n=1013)	10 MG (n=699)	20 MG (n=455)
Gastrointestinal disorders				
Nausea	9%	21%	26%	32%
Diarrhea	6%	7%	7%	7%
Dry mouth	6%	7%	7%	8%
Constipation	3%	3%	5%	6%
Vomiting	1%	3%	5%	6%
Flatulence	1%	1%	3%	1%
Nervous system disorders				
Dizziness	6%	6%	6%	9%
Psychiatric disorders				
Abnormal dreams	1%	<1%	<1%	3%
Skin and subcutaneous tissue disorders				
Pruritus†	1%	1%	2%	3%
Discontinuation	4%	5%	6%	8%

*Based on the rates for 5-, 10-, 15-, and 20-mg doses.[1]
†Includes pruritus generalized.[1]

NAUSEA[1]

- Most common adverse reaction; frequency was dose-related
- Most common adverse reaction reported as a reason for discontinuation
- Typically found to have been mild or moderate in intensity
- Most commonly occurred in the first week of treatment, with 15% to 20% of patients experiencing nausea after 1 to 2 days of treatment
- ~10% of patients taking TRINTELLIX 10 to 20 mg/day still had nausea at the end of the 6- to 8-week studies
- Median duration was 2 weeks

DISCONTINUATION RATES[1]

- In pooled 6- to 8-week clinical studies, discontinuation rates due to adverse reactions were 4%, placebo; 5%, TRINTELLIX 5 mg; 6%, TRINTELLIX 10 mg; and 8%, TRINTELLIX 20 mg
- Nausea was the most common adverse reaction reported as a reason for discontinuation

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Increased Risk of Bleeding:** The use of drugs that interfere with serotonin reuptake inhibition, including TRINTELLIX, may increase the risk of bleeding events, including but not limited to gastrointestinal.

Please see additional Important Safety Information, including Boxed WARNING regarding Suicidal Thoughts and Behaviors, throughout this brochure, and click for Full Prescribing Information.

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Increased Risk of Bleeding (cont'd):** Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Inform patients about the increased risk of bleeding when TRINTELLIX is coadministered with NSAIDs, aspirin, or other drugs that affect coagulation or bleeding. Exposure to SSRIs or SNRIs, particularly in the month before delivery, has been associated with a less than 2-fold increase in the risk of postpartum hemorrhage.
- **Activation of Mania/Hypomania:** In patients with bipolar disorder, treating a depressive episode with TRINTELLIX or another antidepressant may precipitate a mixed/manic episode. Prior to initiating treatment with TRINTELLIX, screen patients for any personal or family history of bipolar disorder, mania, or hypomania.
- **Discontinuation Syndrome:** Adverse reactions have been reported upon abrupt discontinuation of treatment with TRINTELLIX at doses of 15 mg/day and 20 mg/day. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible.
- **Angle-Closure Glaucoma:** The pupillary dilation that occurs following use of many antidepressant drugs, including TRINTELLIX, may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.
- **Hyponatremia:** Hyponatremia has occurred as a result of treatment with serotonergic drugs, including TRINTELLIX, and in many cases appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients and patients taking diuretics or who are otherwise volume-depleted can be at greater risk. Symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. More severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. Discontinue TRINTELLIX in patients with symptomatic hyponatremia and institute appropriate medical intervention.
- **Sexual Dysfunction**: Use of serotonergic antidepressants, including TRINTELLIX, may cause symptoms of sexual dysfunction. In male patients, serotonergic antidepressant use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, use may result in decreased libido and delayed or absent orgasm.

ADVERSE REACTIONS

The most commonly observed adverse reactions for TRINTELLIX in 6- to 8-week placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were: nausea, constipation, and vomiting.

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

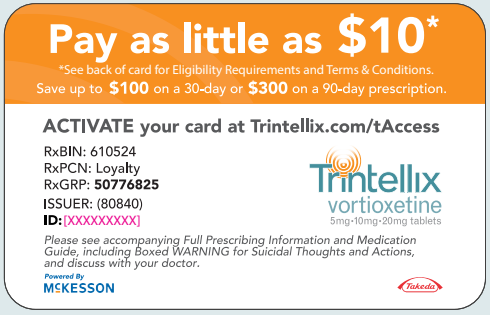
Concomitant administration of TRINTELLIX and strong CYP2D6 inhibitors or strong CYP inducers may require a dose adjustment of TRINTELLIX.

PREGNANCY

Exposure to serotonergic antidepressants, including TRINTELLIX, in late pregnancy may increase the risk for neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN). Monitor neonates who were exposed to TRINTELLIX in the third trimester for PPHN and drug discontinuation syndrome. Use of TRINTELLIX in the month before delivery may be associated with an increased risk of postpartum hemorrhage.

Please see additional Important Safety Information, including Boxed WARNING regarding Suicidal Thoughts and Behaviors, throughout this brochure, and click for Full Prescribing Information.

HELP YOUR ELIGIBLE ADULT PATIENTS SAVE ON THEIR 30- OR 90-DAY PRESCRIPTION*



They can text "TSAVE2" to 36395 to access the TRINTELLIX Savings Card directly on their phone or download it on the website.

*Only commercially insured patients ages 18 and older with a valid prescription are eligible for the TRINTELLIX Savings Card. Savings up to $100 per 30-day or $300 per 90-day prescription. See Savings Card for full Eligibility Requirements and Terms & Conditions.

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OFFER YOUR PATIENTS COMPREHENSIVE RELIEF WITH TRINTELLIX, TODAY

RELIEVED THE OVERALL SYMPTOMS OF MDD[1]

Based on MADRS or HAM-D_{24} total scores vs placebo, as shown in 6 short-term (6- to 8-week) studies.

See details on page 2.

MAINTAINED EFFICACY IN A LONG-TERM STUDY[1,3]

Based on time to recurrence of a depressive episode during the first 28 weeks of the double-blind phase vs placebo.

See details on pages 4-5.

A SWITCH TO TRINTELLIX IMPROVED SSRI-INDUCED SEXUAL DYSFUNCTION WHILE MAINTAINING ANTIDEPRESSANT EFFICACY[1,4]

In well-treated MDD patients experiencing sexual dysfunction.

In MDD efficacy studies, treatment-emergent sexual dysfunction with TRINTELLIX was reported.

See details on pages 6-7.

SCAN TO GET STARTED

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS & BEHAVIORS

- **Antidepressants increased the risk of suicidal thoughts and behaviors 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.**
- **TRINTELLIX is not approved for use in pediatric patients.**

Please see Important Safety Information, including Boxed WARNING regarding Suicidal Thoughts and Behaviors, throughout this brochure, and click for Full Prescribing Information.

References: 1. TRINTELLIX (vortioxetine) prescribing information. Takeda Pharmaceuticals. **2.** Data on file. Takeda Pharmaceuticals. **3.** Thase ME, Jacobsen PL, Hanson E, Xu R, Tolkoff M, Murthy NV. *J Affect Disord.* 2022;303:123-130. **4.** Jacobsen PL, Mahableshwarkar AR, Chen Y, Chrones L, Clayton AH. *J Sex Med.* 2015;12(10):2036-2048. **5.** FDA updates Trintellix® (vortioxetine) label to include data showing improvement in processing speed, an important aspect of cognitive function in acute Major Depressive Disorder (MDD). News release. GlobeNewswire. May 2, 2018. **6.** Costa SL, Genova HM, DeLuca J, Chiaravalloti ND. *Mult Scler.* 2017;23(6):772-789. **7.** McIntyre RS, Lophaven S, Olsen CK. *Int J Neuropsychopharmacol.* 2014;17(10):1557-1567. **8.** Mahableshwarkar AR, Zajecka J, Jacobson W, Chen Y, Keefe RSE. *Neuropsychopharmacology.* 2015;40(8):2025-2037.

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