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**Pharmacology of Trintellix**

**Mechanism of Action**

The mechanism of the antidepressant effect 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; the contribution of these activities to the antidepressant effect has not been established

**Absorption**

Peak plasma concentration: 9, 18, and 33 ng/mL following doses of 5, 10, and 20 mg/day

Peak plasma time: 7-11 hr

**Distribution**

Protein bound: 98%

Vd: 2600 L (extensive extravascular distribution)

**Metabolism**

Extensively metabolized primarily through oxidation via CYP450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 and subsequent glucuronic acid conjugation

CYP2D6 is the primary metabolic pathway

Metabolites: Carboxylic acid metabolite (inactive)

**Elimination**

Half-life: 66 hr

Excretion: 59% urine; 26% feces

**Pharmacogenomics**

Poor metabolizers of CYP2D6 have ~twice the vortioxetine plasma concentration of extensive metabolizers

**Black Box Warnings**

Suicidality

* In short-term studies, antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults (<24 years) taking antidepressants for major depressive disorders and other psychiatric illnesses; this increase was not seen in patients >24 years
* Slight decrease in suicidal thinking was seen in adults >65 years
* In children and young adults, risks must be weighed against the benefits of taking antidepressants
* Patients should be monitored closely for changes in behavior, clinical worsening, and suicidal tendencies; this should be done during initial 1-2 months of therapy and dosage adjustments
* The patient’s family should communicate any abrupt changes in behavior to the healthcare provider
* Worsening behavior and suicidal tendencies that are not part of the presenting symptoms may require discontinuation of therapy; this drug is not approved for use in pediatric patients

**Contraindications**

Hypersensitivity

Coadministration with MAOIs

* Coadministration of MAOIs with vortioxetine or within 3 weeks of discontinuing vortioxetine
* Initiating vortioxetine within 14 days of stopping an MAOI
* Starting vortioxetine in a patient who is being treated with linezolid or IV methylene blue is contraindicated because of an increased risk of serotonin syndrome
* If linezolid or IV methylene blue must be administered, discontinue vortioxetine immediately and monitor for CNS toxicity; monitor for symptoms of serotonin syndrome for 3 weeks or until 24 hours after the last dose of linezolid or methylene blue; may resume vortioxetine 24 hr after last dose of linezolid or methylene blue

**Cautions**

Clinical worsening of depression and suicide risk (see Black Box Warning)

May worsen mania symptoms or activate mania/hypomania in patients with bipolar disorder

Serotonin Syndrome 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 symptoms occur, discontinue therapy and initiate supportive treatment; if concomitant use with other serotonergic drugs is clinically warranted, patients should be made aware of potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases

Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase risk of abnormal bleeding. patients should be cautioned about increased risk of bleeding when vortioxetine is coadministered with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation

Increases risk of hyponatremia and cognitive impairment especially in the elderly or volume depleted patients; hyponatremia can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Angioedema reported with use

Seizures reported; use caution in patients with history of seizure disorders or conditions predisposing to seizures

Risk of mydriasis; may trigger angle closure attack in patients with angle closure glaucoma with anatomically narrow angles without a patent iridectomy

Bone fractures reported with antidepressant treatment; consider possibility of fracture if antidepressant-treated patient presents with unexplained bone pain

Use not recommended in severe hepatic impairment

Discontinuation syndrome may occur with abrupt discontinuation; symptoms may include nausea, vomiting, diminished appetite, tremors, chills diarrhea, headaches, lightheadedness, fatigue, sleep disturbances (ie, insomnia, vivid dreams), and somnolence

#### Contraindicated (8)

* isocarboxazid
* linezolid
* methylene blue
* phenelzine
* rasagiline
* selegiline
* selegiline transdermal
* tranylcypromine

**Adverse Effects**

**>10%**

Nausea (21-32%)

**1-10%**

Diarrhea (7-10%)

Dizziness (6-9%)

Dry mouth (6-8%)

Constipation (3-6%)

Vomiting (3-6%)

Flatulence (1-3%)

Pruritus (1-3%)

Abnormal dreams (<1-3%)

**Postmarketing Reports (rare but to be aware)**

Weight gain

Acute pancreatitis