Indications

LYBALVI is indicated for the treatment of:

- Schizophrenia in adults
- Bipolar I disorder in adults
  - Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate
  - Maintenance monotherapy treatment

Important Safety Information

Boxed Warning: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

Contraindications:

LYBALVI is contraindicated in patients who are using opioids or are undergoing acute opioid withdrawal. If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for the contraindications for these products.

*Source: IQVIA Total Prescriptions (TRx) Data October 2021 – July 2022.[1]

Schizophrenia: LYBALVI TRx grew 1946% (from 96 to 1964). Market leader TRx decreased 5% (from 190,096 to 180,297).

Bipolar I Disorder: LYBALVI TRx grew 2306% (from 71 to 1708). Market leader TRx decreased 3% (from 401,517 to 389,199).

Analysis includes market basket of products that have an indication consistent with an FDA-approved indication for LYBALVI. This information is not intended to suggest clinical comparability of products and should not be seen as making a claim regarding safety or efficacy.

LYBALVI CO-PAY SAVINGS PROGRAM

Commercially insured eligible patients may be able to save on co-pay costs. Terms and Conditions apply.

LEARN MORE AT
LYBALVIHCP.COM

Please see additional Important Safety Information and the Brief Summary of full Prescribing Information, including Boxed Warning, on the following pages.

Important Safety Information

Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis, including stroke, transient ischemia attack, and fatalities. See Boxed Warning.

Precipitation of Severe Opioid Withdrawal in Patients who are Physiologically Dependent on Opioids: LYBALVI can precipitate opioid withdrawal in patients who are dependent on opioids, which can lead to an opioid withdrawal syndrome, sometimes requiring hospitalization. LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids. Explain the risks associated with precipitated withdrawal and the importance of giving an accurate account of last opioid use to patients and caregivers.

Vulnerability to Life-Threatening Opioid Overdose: Attempting to overcome opioid blockade with high or repeated doses of exogenous opioids could lead to life-threatening or fatal opioid intoxication, particularly if LYBALVI therapy is interrupted or discontinued subjecting the patient to high levels of unopposed opioid agonist as the samidorphan blockade wanes. Inform patients of the potential consequences of trying to overcome the opioid blockade and the serious risks of taking opioids concurrently with LYBALVI or while transitioning off LYBALVI. In emergency situations, if a LYBALVI-treated patient requires opioid treatment as part of anesthesia or analgesia, discontinue LYBALVI. Opioids should be administered by properly trained individual(s) and patient should be continuously monitored in a setting equipped and staffed for cardiopulmonary resuscitation. Patients with a history of chronic opioid use prior to treatment with LYBALVI may have decreased opioid tolerance if LYBALVI therapy is interrupted or discontinued. Advise patients that this decreased tolerance may increase the risk of opioid overdose if opioids are resumed at the previously tolerated dosage.

Neuroleptic Malignant Syndrome, a potentially fatal reaction. Signs and symptoms include hyperpyrexia, muscle rigidity, delirium, autonomic instability, elevated creatinine phosphokinase, myoglobinuria (and/or rhabdomyolysis), and acute renal failure. Manage with immediate discontinuation, intensive symptomatic treatment, and close monitoring.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), a potentially fatal condition reported with exposure to olanzapine, a component of LYBALVI. Symptoms include a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. Discontinue if DRESS is suspected.

Metabolic Changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Any patient treated with LYBALVI should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required anti-diabetic treatment despite discontinuation of the suspect drug. Measure weight and assess fasting glucose and lipids when initiating LYBALVI and monitor periodically.

Tardive Dyskinesia (TD): Risk of developing TD (a syndrome of potentially irreversible, involuntary, dyskinetic movements) and the likelihood it will become irreversible increases with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses, or after discontinuation. Given these considerations, LYBALVI should be prescribed in a manner that is most likely to reduce the risk of tardive dyskinesia. If signs and symptoms of TD appear, drug discontinuation should be considered.

Orthostatic Hypotension and Syncope: Monitor orthostatic vital signs in patients who are vulnerable to hypotension, patients with known cardiovascular disease, and patients with cerebrovascular disease.

Falls: LYBALVI may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls, and consequently, fractures or other injuries. Assess patients for risk when using LYBALVI.

Leukopenia, Neutropenia, and Agranulocytosis (including fatal cases): Perform complete blood counts in patients with a history of a clinically significant low white blood cell (WBC) count or history of leukopenia or neutropenia. Discontinue LYBALVI if clinically significant decline in WBC occurs in the absence of other causative factors.

Dysphagia: Use LYBALVI with caution in patients at risk for aspiration.

Seizures: Use LYBALVI with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: Because LYBALVI may cause somnolence, impair judgment, thinking, or motor skills, caution patients about operating hazardous machinery, including motor vehicles, until they are certain that LYBALVI does not affect them adversely.

Body Temperature Dysregulation: Use LYBALVI with caution in patients who may experience conditions that increase core body temperature (e.g., strenuous exercise, extreme heat, dehydration, or concomitant use with anticholinergics).

Anticholinergic (Antimuscarinic) Effects: Olanzapine, a component of LYBALVI, was associated with constipation, dry mouth, and tachycardia. Use LYBALVI with caution with other anticholinergic medications and in patients with urinary retention, prostatic hypertrophy, constipation, paralytic ileus or related conditions. In postmarketing experience, the risk for severe adverse reactions (including fatalities) was increased with concomitant use of anticholinergic medications.

Hyperprolactinemia: LYBALVI elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

Risks Associated with Combination Treatment with Lithium or Valproate: If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for a description of the risks for these products.

Most common adverse reactions observed in clinical trials were:

- *Schizophrenia (LYBALVI):* weight increased, somnolence, dry mouth, and headache
- *Bipolar I Disorder, Manic or Mixed Episodes (olanzapine):* asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor
- *Bipolar I Disorder, Manic or Mixed Episodes, adjunct to Lithium or Valproate (olanzapine):* dry mouth, dyspepsia, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia

Concomitant Medication: LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. Concomitant use of LYBALVI is not recommended with strong CYP3A4 inducers, levodopa and dopamine agonists. Reduce dosage of LYBALVI when using with strong CYP1A2 inhibitors. Increase dosage of LYBALVI with CYP1A2 inducers. Use caution with diazepam, alcohol, other CNS acting drugs, or in patients receiving anticholinergic (antimuscarinic) medications. Monitor blood pressure and reduce dosage of antihypertensive drug in accordance with its approved product labeling.

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with LYBALVI. Inform patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LYBALVI during pregnancy.

Renal Impairment: LYBALVI is not recommended for patients with end-stage renal disease (eGFR of <15 mL/minute/1.73 m^2).

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes at 1-888-235-8008 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the Brief Summary of full Prescribing Information, including Boxed Warning, for LYBALVI on the following pages.

References: 1. IQVIA TRx. [Estimate derived from the use of information under license from the following IQVIA information service: Source of Business for the period October 2021 – July 2022. IQVIA expressly reserves all rights, including rights of copying, distribution and republication.] **2.** LYBALVI [prescribing information]. Waltham, MA: Alkermes, Inc.; 2021.

LYBALVI® (olanzapine and samidorphan) tablets, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

(For complete details, see full Prescribing Information)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

INDICATIONS AND USAGE

LYBALVI is indicated for the treatment of:

- Schizophrenia in adults
- Bipolar I disorder in adults
  - Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate
  - Maintenance monotherapy treatment

CONTRAINDICATIONS

LYBALVI is contraindicated in patients:

- who are using opioids
- who are undergoing acute opioid withdrawal

If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for the contraindications for these products.

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than in placebo-treated patients (3.5% vs 1.5%, respectively). Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis: Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse reactions in patients treated with olanzapine compared to patients treated with placebo. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

Precipitation of Severe Opioid Withdrawal in Patients Who Are Physiologically Dependent on Opioids: Samidorphan, an opioid antagonist that is a component of LYBALVI, can precipitate opioid withdrawal in patients who are dependent on opioids, which can lead to an opioid withdrawal syndrome, sometimes requiring hospitalization. Therefore, LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids. Explain the risks associated with precipitated withdrawal and the importance of giving an accurate account of last opioid use to patients and caregivers.

Vulnerability to Life-Threatening Opioid Overdose

Risk of Opioid Overdose from Attempts to Overcome Samidorphan Blockade:

LYBALVI contains samidorphan, an opioid antagonist. Attempting to overcome LYBALVI's opioid blockade with high or repeated doses of exogenous opioids (e.g., because of ineffective analgesia or opioid withdrawal symptoms) could lead to life-threatening or fatal opioid intoxication (e.g., respiratory arrest, circulatory collapse), particularly if LYBALVI therapy is interrupted or discontinued, subjecting the patient to high levels of unopposed opioid agonist as the samidorphan blockade wanes. Inform patients of the potential consequences of trying to overcome the opioid blockade and the serious risks of taking opioids concurrently with LYBALVI or while transitioning off LYBALVI.

In emergency situations, if a LYBALVI-treated patient requires opioid treatment as part of anesthesia or analgesia:

- Discontinue LYBALVI,
- Opioids should be administered by individual(s) trained in the use of anesthetic drugs and the management of the respiratory effects of opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation, and
- Appropriately trained personnel should continuously monitor the patient in a setting equipped and staffed for cardiopulmonary resuscitation.

For recommendations on starting opioids in LYBALVI-treated patients in non-emergent situations, see DRUG INTERACTIONS section.

Risk of Resuming Opioids in Patients with Prior Opioid Use

Patients with a history of chronic opioid use prior to treatment with LYBALVI may have decreased opioid tolerance if LYBALVI therapy is interrupted or discontinued. Advise patients that this decreased tolerance may increase the risk of opioid overdose if opioids are resumed at the previously tolerated dosage.

Neuroleptic Malignant Syndrome: Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue LYBALVI and provide intensive symptomatic treatment and monitoring.

Drug Reaction with Eosinophilia and Systemic Symptoms: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with exposure to olanzapine, a component of LYBALVI. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. DRESS is sometimes fatal. Discontinue LYBALVI if DRESS is suspected.

Metabolic Changes: Atypical antipsychotic drugs, including LYBALVI, have been associated with metabolic changes that include hyperglycemia, diabetes mellitus, dyslipidemia, and body weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Any patient treated with LYBALVI should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with LYBALVI should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required anti-diabetic treatment despite discontinuation of the suspect drug. Patients starting treatment with LYBALVI should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

Antipsychotics have caused adverse alterations in lipids. Patients starting treatment with LYBALVI should undergo fasting lipid profile testing at the beginning of treatment and periodically during treatment.

Weight gain has been observed with use of antipsychotics. Monitor weight prior to initiating LYBALVI and frequently thereafter.

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible increases with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, LYBALVI should be prescribed in a manner that is most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and 2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient on LYBALVI, drug discontinuation should be considered. However, some patients may require treatment with LYBALVI despite the presence of the syndrome.

Orthostatic Hypotension and Syncope: Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose titration and when increasing the dose. In the 4-week, placebo-controlled study, from analysis of the vital signs data, rates of orthostatic hypotension were less than 2% in LYBALVI- and placebo-, and olanzapine-treated patients. In the 24-week, olanzapine-controlled study, from analysis of the vital signs data, rates of orthostatic hypotension in LYBALVI-treated patients were 3.7%, compared to 0.4% in olanzapine-treated patients.

Monitor orthostatic vital signs in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypovolemia, concomitant treatment with antihypertensive medications or CNS depressants, patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. LYBALVI has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from the premarketing clinical trials.

Falls: Antipsychotics, including LYBALVI, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including LYBALVI. Agranulocytosis (including fatal cases) has been reported with other agents in this class.

Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia. In patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of LYBALVI at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue LYBALVI in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) and follow their WBC until recovery.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including LYBALVI, should be used cautiously in patients at risk for aspiration.

Seizures: Like other antipsychotic drugs, LYBALVI may cause seizures. This risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

Potential for Cognitive and Motor Impairment: LYBALVI, like other antipsychotics, may cause somnolence and has the potential to impair judgment, thinking, or motor skills. In a LYBALVI placebo-controlled study, somnolence occurred in 9% of LYBALVI-treated patients compared to 2.2% in patients treated with placebo.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that LYBALVI therapy does not affect them adversely.

Body Temperature Dysregulation: Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use LYBALVI with caution in patients who may experience these conditions.

Anticholinergic (Antimuscarinic) Effects: Olanzapine, a component of LYBALVI, exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with oral olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Such adverse reactions were not often the basis for discontinuations, but LYBALVI should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, constipation, or a history of paralytic ileus or related conditions. In postmarketing experience, the risk for severe adverse reactions (including fatalities) was increased with concomitant use of anticholinergic medications.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, olanzapine, a component of LYBALVI, elevates prolactin levels, and the elevation can persist during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously-detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

In the 4-week placebo-controlled trial, shifts from normal to high prolactin values (>30 ng/mL for females; >20 ng/mL for males) occurred in 41.4% of females and 32.9% of males treated with LYBALVI, in 56.1% of females and 37.1% of males treated with olanzapine, and in 10% of females and 4.8% of males treated with placebo.

In the 24-week, olanzapine-controlled study, shifts from normal to high prolactin values occurred in 32.9% of females and 22.5% of males treated with LYBALVI, and in 41.7% of females and 28.5% of males treated with olanzapine.

Risks Associated with Combination Treatment with Lithium or Valproate: If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for a description of the risks for these products including, but not limited to, the warnings and precautions for lithium or valproate.

ADVERSE REACTIONS

Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Patients with Schizophrenia:

Patient Exposure

The safety of LYBALVI was evaluated in 1262 patients (18 to 67 years of age) diagnosed with schizophrenia in four double-blind, controlled studies and three long-term safety extension studies of up to 3 years of duration. This experience corresponds to approximately 910 person-years. In these studies, there were a total of 663 patients exposed to LYBALVI for at least 6 months, and 386 patients for at least one year.

Adverse Reactions in the Short-Term (4 week) Placebo-Controlled Trial in Adults with Schizophrenia

The most common adverse reactions (incidence of at least 5% of patients exposed to LYBALVI and greater than twice the rate of placebo) are weight increased, somnolence, dry mouth, and headache.

Adverse reactions associated with the use of LYBALVI (incidence of 2% or greater and greater than in placebo-treated patients) are shown in Table 1.

Table 1: Adverse Reactions Reported in ≥2% of LYBALVI-Treated Patients and Greater than Placebo in a 4-Week Schizophrenia Trial

Adverse Reaction	Placebo (N=134) %	LYBALVI (10 mg/10 mg, 20 mg/10 mg) (N=134) %
Weight increased	3	19
Somnolence	2	9
Dry mouth	1	7
Headache	3	6
Blood insulin increased	1	3
Sedation	0	2
Dizziness	1	2
Neutrophil count decreased	0	2

Adverse reactions that led to discontinuation in LYBALVI-treated patients in the short-term placebo-controlled trial in adults with schizophrenia include schizophrenia (1%) and abnormal liver function tests (1%).

Adverse Reactions in the Long-Term (24-week), Active-Controlled Trial in Adults with Schizophrenia

In the 24-week, olanzapine-controlled trial in patients with stable schizophrenia, adverse reactions associated with the use of LYBALVI (incidence of 2% or greater) include: weight increased (25%), somnolence (21%), dry mouth (13%), increased appetite (11%), waist circumference increased (6%), blood creatine phosphokinase increased (5%), headache (4%), lethargy (4%), sedation (4%), akathisia (3%), alanine aminotransferase increased (3%), aspartate aminotransferase increased (3%), constipation (3%), dizziness (3%), fatigue (3%), nausea (3%), blood pressure increased (3%), neutrophil count decreased (3%), blood insulin increased (2%), weight decreased (2%), and dyslipidemia (2%).

Adverse reactions that led to LYBALVI treatment discontinuation in more than one patient include somnolence (2%), weight increased (2%), neutropenia (2%), glycosylated hemoglobin increased (1%), schizophrenia (1%), and liver function test abnormal (1%).

Hyperglycemia: Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of

the 2 highest serum concentrations was 15.0 mg/dL. Hyperglycemia, as defined by fasting glucose ≥126 mg/dL, has been observed in patients treated with LYBALVI.

In the 4-week placebo-controlled trial in adult patients with schizophrenia, shifts in fasting glucose from normal to high occurred in 4% of patients treated with LYBALVI, 1% of patients treated with olanzapine, and no patients treated with placebo.

In the 24-week olanzapine-controlled trial, patients treated with LYBALVI were more likely to experience abnormal shifts in glycemic parameters than patients treated with olanzapine (Table 2).

Table 2: Changes in Glycemic Parameters in a 24-Week Trial of Patients with Schizophrenia

	LYBALVI	Olanzapine
Proportion of Patients with Shifts, % (n/N)*		
Glucose Normal to High (<100 mg/dL to ≥126 mg/dL)	12 (26/223)	8 (18/219)
Impaired (≥100 mg/dL and <126 mg/dL) to High (≥126 mg/dL)	24 (9/38)	11 (5/47)
Increase ≥10 mg/dL	66 (174/265)	57 (154/270)
Hemoglobin A1c Normal (<5.7%) to Impaired (≥5.7% and <6.5%)	42 (86/204)	35 (68/197)
Normal to High (<5.7% to ≥6.5%)	0.5 (1/204)	1.5 (3/197)
Impaired (≥5.7% and <6.5%) to High (≥6.5%)	9.5 (6/63)	9.2 (7/76)

* n: number of patients with reported abnormal shifts; N: number of patients who had assessments at both baseline and endpoint for mean change, or normal at baseline and at least 1 post-baseline assessment for shift.

Dyslipidemia: In the 4-week, placebo-controlled trial in adult patients with schizophrenia, shifts in fasting triglycerides from normal to high occurred in 14% of patients treated with LYBALVI and 4% of patients treated with placebo.

In the 24-week olanzapine-controlled study, mean changes in fasting total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were similar in patients treated with LYBALVI and in patients treated with olanzapine.

Weight Gain: In the 4-week placebo-controlled study in adult patients with schizophrenia, mean changes in weight, and proportion of patients with ≥7% weight increase, were greater in patients treated with LYBALVI and olanzapine than in patients on placebo. In that study, mean weight gain was 3.0 kg in patients treated with LYBALVI, 2.4 kg in patients treated with olanzapine, and 0.2 kg in patients treated with placebo. The proportion of patients with ≥7% weight increase was 26% in patients treated with LYBALVI, 20% in patients treated with olanzapine, and 5% in patients treated with placebo.

In the 24-week trial, LYBALVI-treated patients gained on average 4.2% of baseline body weight. The proportion of patients treated with LYBALVI with ≥10% body weight gain was 17.8%.

Extrapyramidal Symptoms: In the 4-week placebo-controlled trial in adult patients with schizophrenia, patients were assessed using the Simpson-Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS) (total score ranges from 1 to 14), the Barnes Akathisia Rating Scale (BARS) for akathisia (total score ranges from 0 to 14), and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesias (total score ranges from 0 to 28). The mean changes from baseline to last study visit for the SAS, BARS, and AIMS was similar in LYBALVI-treated patients and in placebo-treated patients. The mean changes for LYBALVI- vs placebo-treated patients were 0.00 vs -0.2 for AIMS, 0.0 vs -0.1 for BARS, and 0.0 vs -0.3 for SAS, respectively. The rate of parkinsonism (SAS total score >3) was lower in patients treated with LYBALVI (4%) compared to those on placebo (10%). The rates of akathisia (BARS global clinical assessment score ≥2) and dyskinesia (AIMS score ≥3 on any of the first 7 items, or a score ≥2 on two or more of any of the first 7 items) were similar in patients treated with LYBALVI and in those on placebo. Rates of akathisia were 6.0% and 8.2% in patients treated with LYBALVI and placebo, respectively, and the rate of dyskinesia was 1.5% both in LYBALVI-treated and in placebo-treated patients.

The frequency of reported adverse reactions related to extrapyramidal symptoms, including akathisia, restlessness, muscle spasms, bradykinesia, tremor, extrapyramidal disorder, and parkinsonism was 2% both in LYBALVI-treated and in placebo-treated patients.

In the 24-week active-controlled trial, the mean change from baseline to the last visit for the SAS, BARS, and AIMS was similar in LYBALVI-treated patients and in those treated with the active control. Extrapyramidal adverse reactions, including parkinsonism, akathisia, and dyskinesia, had a similar incidence in LYBALVI-treated patients and in those treated with the active control: any extrapyramidal symptom was 8%, akathisia was 3%.

Dystonia: Symptoms of dystonia, (prolonged abnormal contractions of muscle groups) may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. Although these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Adverse Reactions in Patients with Bipolar Disorder: The safety of LYBALVI for the treatment of bipolar I disorder (mixed or manic) monotherapy and adjunct to lithium or valproate relies on information from adequate and well-controlled studies of olanzapine tablets in bipolar I disorder.

The most common adverse reactions (incidence of at least 5% of patients exposed to olanzapine and greater than or equal to twice the rate of placebo) from short-term trials of olanzapine (manic or mixed episodes) are somnolence, dry mouth, dizziness, asthenia, constipation, dyspepsia, increased appetite, and tremor.

The most common adverse reactions (incidence of at least 5% of patients exposed to olanzapine and greater than or equal to twice the rate of placebo) from short-term trials of olanzapine as adjunct to lithium or valproate (manic or mixed episodes) are dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of olanzapine. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

- allergic reactions (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria)
- cholestatic or mixed liver injury, hepatitis, jaundice
- diabetic coma, diabetic ketoacidosis
- discontinuation reaction (diaphoresis, nausea or vomiting)
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- hyperlipidemia (random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported)
- neutropenia
- pancreatitis
- priapism
- rash
- restless legs syndrome
- rhabdomyolysis
- salivary hypersecretion
- stuttering[1]
- venous thromboembolic events (including pulmonary embolism and deep venous thrombosis)

[1] Stuttering was only studied in oral and long-acting injection (LAI) formulations.

DRUG INTERACTIONS

Effects of Other Drugs on LYBALVI: Table 3 describes clinically significant drug interactions where the concomitant use of other drugs affects LYBALVI.

Table 3: Effects of Other Drugs on LYBALVI

Strong CYP3A4 Inducer	
Clinical Implication:	Coadministration of LYBALVI with a strong CYP3A4 inducer decreases AUC_{inf} of olanzapine and samidorphan which may reduce LYBALVI efficacy.
Prevention or Management:	Concomitant use of LYBALVI with strong CYP3A4 inducers is not recommended.
Strong CYP1A2 Inhibitor	
Clinical Implication:	Concomitant use of LYBALVI with a strong CYP1A2 inhibitor increases olanzapine AUC and C_{max}, which may increase risk of LYBALVI adverse reactions.
Prevention or Management:	Consider reducing the dosage of the olanzapine component in LYBALVI when used concomitantly with strong CYP1A2 inhibitors.
CYP1A2 Inducer	
Clinical Implication:	Concomitant use of LYBALVI with CYP1A2 inducers decreases olanzapine exposure, which may reduce LYBALVI efficacy.

Table 3: Effects of Other Drugs on LYBALVI (cont'd)

Prevention or Management:	Consider increasing the dosage of the olanzapine component in LYBALVI when used concomitantly with CYP1A2 inducers.
Diazepam, Alcohol and CNS Acting Drugs	
Clinical Implication:	Concomitant use of diazepam, alcohol, or other CNS acting drugs with LYBALVI may potentiate orthostatic hypotension observed with olanzapine.
Prevention or Management:	LYBALVI should be used with caution in patients receiving concomitantly diazepam or other CNS acting drugs, or using alcohol.
Anticholinergic Drugs	
Clinical Implication:	Concomitant treatment with olanzapine and other drugs with anticholinergic activity can increase the risk for severe gastrointestinal adverse reactions related to hypomotility.
Prevention or Management:	Consider increasing the dosage of the olanzapine component in LYBALVI when used concomitantly with CYP1A2 inducers.

Effects of LYBALVI on Other Drugs: Table 4 describes clinically significant drug interactions where concomitant use of LYBALVI affects other drugs.

Table 4: Effects of LYBALVI on Other Drugs

Antihypertensive Agents	
Clinical Implication:	LYBALVI may enhance the effects of certain antihypertensive agents.
Prevention or Management:	Monitor blood pressure and reduce dosage of antihypertensive drug in accordance with its approved product labeling.
Levodopa and Dopamine Agonists	
Clinical Implication:	LYBALVI may antagonize the effects of levodopa and dopamine agonists.
Prevention or Management:	Concomitant use of LYBALVI is not recommended with levodopa and dopamine agonists.

Opioids: LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal.

LYBALVI increases the risk of precipitating acute opioid withdrawal in patients who are dependent on opioids. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from the last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids.

In *emergency* situations, if a LYBALVI-treated patient requires opioid treatment for anesthesia or analgesia, discontinue LYBALVI. The opioid should be administered by properly trained individual(s), and the patient should be properly monitored in a setting equipped and staffed for cardiopulmonary resuscitation.

In *non-emergency* situations, if a LYBALVI-treated patient is expected to require opioid treatment (e.g., for analgesia during or after an elective surgical procedure) discontinue LYBALVI at least 5 days before opioid treatment and start olanzapine or another antipsychotic, if needed.

Given that LYBALVI contains samidorphan, an opioid antagonist, opioid treatment may be less effective or ineffective shortly after LYBALVI discontinuation because of the presence of samidorphan.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including LYBALVI, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit https://womensmentalhealth.org/research/pregnancyregistry/atypicalantipsychotic/.

Risk Summary: Neonates exposed to antipsychotic drugs, including the olanzapine component of LYBALVI, during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Overall published epidemiologic studies of pregnant women exposed to olanzapine have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no available data on the use of samidorphan or the combination of olanzapine and samidorphan in pregnant women to determine a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including LYBALVI, during pregnancy.

LYBALVI

In an animal reproduction study, oral administration of olanzapine and samidorphan to pregnant rats during the period of organogenesis produced adverse effects on embryofetal development and fetal toxicity at maternally toxic doses that are 6 times and >400 times the maximum recommended human dose (MRHD) of 20 mg/10 mg olanzapine/samidorphan in LYBALVI, respectively based on AUC. There were no adverse effects on embryofetal development at doses of olanzapine and samidorphan that are approximately 1 and 80 times, respectively, the MRHD based on AUC.

Olanzapine

In animal reproduction studies, there was no evidence of malformations in rats or rabbits when orally administered olanzapine at doses up to 9 and 30 times the MRHD dose (20 mg) based on mg/m^2 body surface area, respectively. In an oral rat embryofetal developmental toxicity study, early resorptions and increased numbers of nonviable fetuses were observed at a dose 9 times the MRHD based on mg/m^2 body surface area and gestation was prolonged at 5 times the MRHD based on mg/m^2 body surface area. In an oral rabbit embryofetal developmental toxicity study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of olanzapine which is 30 times the MRHD based on mg/m^2 body surface area.

Samidorphan

In animal reproduction studies, oral administration of samidorphan to pregnant rats and rabbits during the period of organogenesis caused fetal toxicities in rats only at maternally toxic doses that are >248 times the human exposure at the MRHD of 10 mg/day based on AUC. Oral administration of samidorphan to pregnant rats during pregnancy and lactation resulted in lower pup survival and decreased pup weights at 188 times the human exposure at the MRHD based on AUC.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryofetal Risk

There is risk to the mother from untreated schizophrenia or bipolar I disorder, including increased risk of relapse, hospitalization and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/Neonatal Risks

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including the olanzapine component of LYBALVI, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects.

Animal Data

LYBALVI

Olanzapine and samidorphan were orally administered to pregnant rats during the period of organogenesis at doses of 0.5/10, 2/50, 6/200, and 0/200 mg/kg/day (olanzapine/samidorphan) which are approximately <1/10 times to 6/448 times the MRHD of 20 mg/10 mg, olanzapine/samidorphan, respectively, based on AUC. Maternal toxicity consisting of decreased body weight and food consumption was observed at all dose levels. Administration of samidorphan alone (200 mg/kg/day) and 6/200 mg/kg/day olanzapine/samidorphan decreased mean fetal body weights, increased litter incidence of bent ribs and bent scapula; however, the incidence of bent scapula and bent ribs was not increased when samidorphan was administered in combination with olanzapine compared to the incidence with samidorphan alone. Administration of olanzapine/samidorphan at 6/200 mg/kg/day also increased resorptions and post-implantation loss, with correlating lower mean viable fetuses and litter size. The no observed adverse effect level (NOAEL) for embryofetal development is 2/50 mg/kg/day, which is approximately 1/80 times the MRHD of 20 mg/10 mg olanzapine/samidorphan respectively, based on AUC.

Olanzapine

Olanzapine was orally administered to pregnant rats and rabbits during the period of organogenesis at doses up to 18 mg/kg/day in rats and at doses up to 30 mg/kg/day in rabbits (9 times and 30 times the MRHD of 20 mg/day based on mg/m^2 body surface area, respectively), and no evidence of malformations was observed. In an oral rat embryofetal developmental toxicity study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD based on mg/m^2 body surface area). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD based on mg/m^2 body surface area). In an oral rabbit embryofetal developmental toxicity study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of olanzapine at 30 mg/kg/day (30 times the MRHD based on mg/m^2 body surface area).

Samidorphan

Samidorphan was orally administered to pregnant rats during the period of organogenesis at doses of 25, 100, and 300 mg/kg/day, which are approximately 29 to 742 times the MRHD of 10 mg/day based on AUC. Samidorphan was associated with an increased incidence of skeletal variations (unossified sternebrae and bent ribs) at maternally toxic doses of ≥100 mg/kg/day, and skeletal malformations (bent or misshapen forelimbs, hindlimbs, and/or scapula) at 300 mg/kg/day which are >248 and 742 times the MRHD based on AUC, respectively. The NOAEL for embryofetal development is 25 mg/kg/day, which is approximately 29 times the MRHD based on AUC.

Samidorphan did not cause adverse effects on embryofetal development when orally administered to pregnant rabbits during the period of organogenesis at doses of 10, 30, and 90 mg/kg/day, which are up to approximately 143 times the MRHD based on AUC.

Samidorphan was orally administered to pregnant rats during pregnancy and lactation at doses of 10, 30, or 100 mg/kg/day, which are approximately 7 to 188 times the MRHD based on AUC. Reduced pup survival, lower birth weights, and decreased pup body weight gains were observed at 100 mg/kg/day, which is 188 times the MRHD based on AUC. The NOAEL of 30 mg/kg/day is approximately 36 times the MRHD based on AUC. There were no adverse effects on pup developmental landmarks, learning, memory, reflexes, or fertility.

Lactation

Risk Summary: Olanzapine is present in human milk. There are reports of excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements) in infants exposed to olanzapine through breast milk. There is no information on the effects of olanzapine on milk production. There are no data on the presence of samidorphan or the combination of olanzapine and samidorphan in human milk, the effects on the breastfed infant or the effects on milk production. When samidorphan was administered to lactating rats, samidorphan and a metabolite were detected in the plasma of nursing pups, likely due to the presence of samidorphan in milk. Infants exposed to LYBALVI should be monitored for excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements).

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for LYBALVI and any potential adverse effects on the breastfed infant from LYBALVI or from the underlying maternal condition.

Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of olanzapine (D2 antagonism), treatment with LYBALVI may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential.

Pediatric Use: The safety and effectiveness of LYBALVI have not been established in pediatric patients.

Geriatric Use: Clinical studies of LYBALVI did not include sufficient numbers of patients 65 years of age and older to determine whether they responded differently than younger adult patients.

Olanzapine: Of the 2,500 patients in premarketing clinical studies with orally administered olanzapine, 11% (263) were 65 years of age or over. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo.

- In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine, compared to patients treated with placebo.
- In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1,184), the following adverse reactions were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than in placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse reactions was greater with olanzapine than with placebo (13% vs 7%).

Consider a lower dosage of the olanzapine component of LYBALVI in geriatric patients who may have decreased clearance or an exaggerated pharmacodynamic response to olanzapine (e.g., oversedation).

Hepatic Impairment: Olanzapine and samidorphan plasma exposures were found to be higher in subjects with moderate hepatic impairment than in subjects with normal hepatic function. The effect of severe hepatic impairment was not studied. The higher plasma exposure in patients with moderate hepatic impairment was not expected to be clinically relevant. No dose adjustment of LYBALVI is needed in patients with hepatic impairment.

Renal Impairment: Plasma exposure to olanzapine and samidorphan was higher in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m^2) compared to those with normal renal function. No dose adjustment of LYBALVI is needed in patients with mild (eGFR 60 to 89 mL/minute/1.73 m^2), moderate (eGFR 30 to 59 mL/minute/1.73 m^2), or severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m^2).

The effect of LYBALVI in patients with end-stage renal disorder was not studied. LYBALVI is not recommended for patients with end-stage renal disorder (eGFR of <15 mL/minute/1.73 m^2).

OVERDOSAGE

Human Experience: There is limited clinical experience with overdose with LYBALVI. In premarketing clinical trials of LYBALVI involving 861 patients, overdose of LYBALVI was identified in 7 patients. This included 4 patients with accidental overdose, 2 with intentional overdose, and 1 due to a medication administration error. None of the reported overdoses was associated with a fatal outcome. There was a reported ingestion of 11 tablets of LYBALVI 10 mg/10 mg (5.5 times and 11 times the maximum recommended daily dosage of the olanzapine and samidorphan components of LYBALVI, respectively). The patient was found unresponsive and admitted to the hospital. Medical treatment included fluids, electrolytes, a diuretic, and a detoxicant; the patient stabilized within 2 days.

In postmarketing reports of overdose with olanzapine, a component of LYBALVI, symptoms included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Less commonly reported symptoms include: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and 1 patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of approximately 2,000 mg.

Management of Overdose: No specific antidotes for LYBALVI are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an overdose occurs, consult a certified Poison Control Center (1-800-222-1222) for additional overdosage management recommendations.

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-888-235-8008 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

This Brief Summary is based on LYBALVI full Prescribing Information (revised: May 2021).

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Assistant/Associate/Professor of Clinical Pediatric Psychiatry

Hiring Department: UICOMP-Pediatrics
Location: Peoria, IL USA
Requisition ID: 1014947
Posting Close Date: 1/18/2023

The University of Illinois College of Medicine at Peoria (UICOMP) seeks a Pediatric Psychiatry physician for a position at the level of Professor, Associate Professor or Assistant Professor to enhance an important clinical program.

Pediatric Psychiatry positions require candidates who are BC in Psychiatry and have completed 3 years in residency and 3 years in fellowship training in Pediatric Psychiatry. Candidates with scholarly and research interests are highly desirable, along with experience in teaching medical students and residents.

Position Summary
Provide outpatient diagnostic and management services for patients in the region with general Psychiatry needs and participate in undergraduate, graduate and continuing education programs of the Department.

Duties & Responsibilities
- Responsibilities – Psychiatrist
- Participate in undergraduate, graduate and continuing education programs of the Department
- Provide outpatient diagnostic and management services for patients in the region with general Psychiatry needs
- Provide inpatient Psychiatry consultation for children
- Organize and conduct research programs in Child Psychiatry
- Perform other duties of a University faculty member including committee assignments, curriculum development, student counseling, and administration.

UICOMP is one of the regional campuses that make up the nation's largest public medical school. The Peoria campus is known among students for its small class sizes, rigorous curriculum and hands-on clerkships; to residents and fellows for the strong academic setting, large referral base and exceptional facilities; and by physicians seeking the ideal combination of teaching and practicing medicine in a research-based university setting.

UICOMP's main clinical partner is OSF Healthcare Children's Hospital of Illinois (CHOI), a 144-bed, full-service hospital, with physicians in more than 140 subspecialties. Located on the campus of OSF St. Francis Medical Center, it's the pediatric teaching affiliate of UICOMP, the state's only major pediatric teaching hospital outside Chicago—and home to groundbreaking pediatric research in medicine. The hospital is also proud to house the St. Jude Midwest Affiliate, which brings some of the care and services offered by St. Jude in Memphis to central Illinois.

Malpractice insurance is provided by the University of Illinois system and an excellent benefits package available including vacations, sick time, CME, health and life insurance and retirement plan.

Minimum Qualifications
- Eligible for licensure in Illinois
- Board Certified in Psychiatry
- Board Certified/Board Eligible in Pediatric Psychiatry

For fullest consideration please submit your application by 12/16/2022 at:

https://uic.csod.com/ux/ats/careersite/1/home/requisition/1804?c=uic

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The Faculty of Medicine of the University of Geneva and the University Hospitals of Geneva are seeking applications for the position of a

Full or Associate Professor, Head of the Division of liaison psychiatry and crisis intervention

CHARGE: This is a joint University Hospital and Faculty position as Head of the Division of liaison psychiatry and crisis intervention including a part-time appointment as professor. The position is attached to the academic and hospital Departments of Psychiatry.

The candidate should have an excellent clinical track record in psychiatry and outstanding leadership, communication and managerial skills to lead a large Division with a wide range of medical activities. The Division assures the consultations of liaison psychiatry for all inpatient units of the University Hospitals of Geneva. It also includes an inpatient unit for patients with medical and psychiatric comorbidities and a crisis intervention unit. In addition, the Division proposes outpatient consultations of liaison psychiatry, a program for eating disorders and a consultation of psychotraumatology. Finally, the head of the Division is responsible for the link between the Department of Psychiatry and the unit of emergency psychiatry which is part of the emergency Division. The candidate will continue and further develop collaborations with the other Divisions of the Department of Psychiatry and the other Departments of the HUG.

The successful candidate will possess the ability to conduct high-level research and have proven competence in team management , mentoring and medical education at both undergraduate and postgraduate levels.

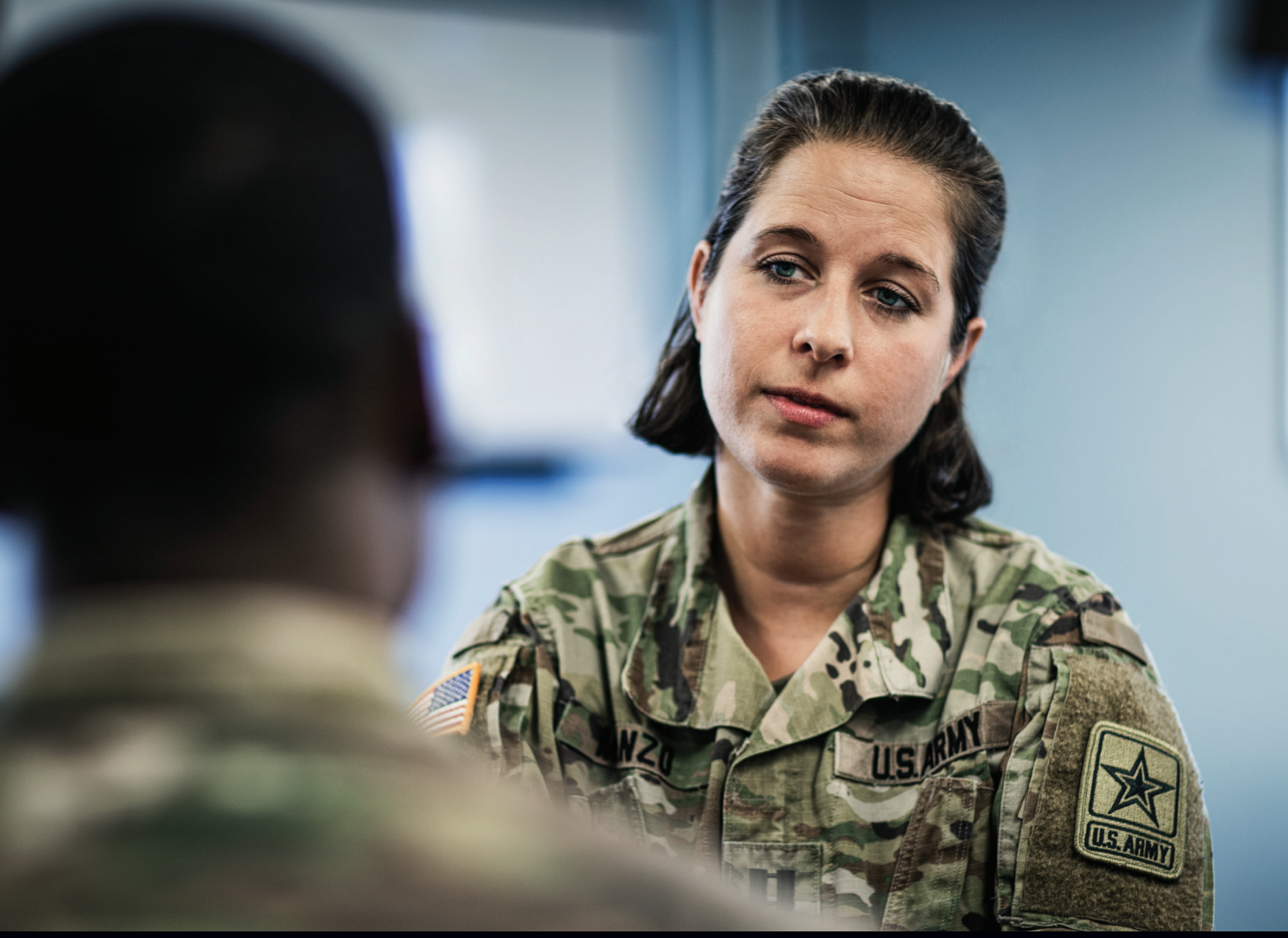
TITLES AND QUALIFICATIONS REQUIRED:
- M.D. title and board certification in Psychiatry and Psychotherapy, or equivalent, are required.
- Good knowledge of French.
- Relevant experience as an independent investigator and teacher
- Publications in leading peer-reviewed journals.

STARTING DATE: October 1st 2023, or upon agreement

For detailed application guidelines, contact:
viviane.burghardt@unige.ch

Mandatory online registration before December 31st 2022 at **http://www.unige.ch/academ**

The University is an equal opportunities employer and particularly welcomes applications from women



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AH2203

NOT JUST ANOTHER ANTIDEPRESSANT

Auvelity is a rapid-acting oral antidepressant with proven efficacy at Week 1[1]*

INDICATION

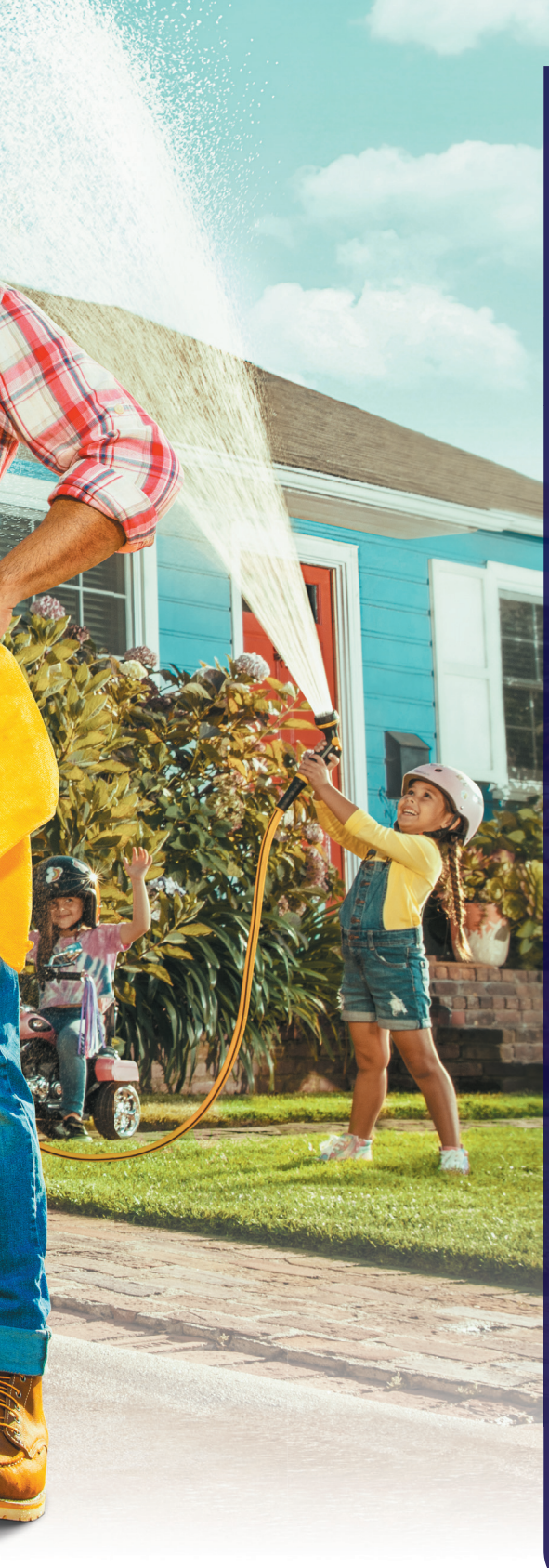
Auvelity is indicated for the treatment of major depressive disorder (MDD) in adults.

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS AND 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 emergence of suicidal thoughts and behaviors.**
- **Auvelity is not approved for use in pediatric patients.**

Please see additional Important Safety Information and the Brief Summary of Prescribing Information on the following pages, including **Boxed Warning** for suicidal thoughts and behaviors.



Auvelity™

(dextromethorphan HBr and bupropion HCl)
extended-release tablets 45mg/105mg

Auvelity uses a new approach to treat MDD that is different from other oral antidepressants approved in more than 60 years[1-3†]

Auvelity is the first and only oral NMDA receptor antagonist for MDD[1-3]

Symptom improvement at Week 1 and sustained at Week 6*

- Patients taking Auvelity had significant change from baseline in the MADRS total score at Week 6 vs placebo (primary endpoint: LS mean change of -12.1 vs -15.9; *P*=0.002).[1,4]

Rapid remission starting at Week 2*

- Significantly more patients achieved remission with Auvelity at Week 2 vs placebo (key secondary endpoint: 17% (24/142) vs 8% (12/159); *P*=0.013).[4]

Demonstrated safety profile in controlled and open-label studies*‡

- The most common adverse reactions in a 6-week study (≥5% and >2x placebo) were: dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis.[1]
- Long-term safety up to 1 year in an open-label study was consistent with controlled studies.[1,5-7]

Explore the difference at AuvelityHCP.com

Actor Portrayal

*GEMINI Phase 3 study evaluated Auvelity vs placebo in 327 patients (N=163 Auvelity and N=164 placebo) with MDD for 6 weeks. N denotes randomized patients. The mITT population, defined as all randomized patients who took at least 1 dose of study drug and had at least 1 post-baseline assessment, was n=156 Auvelity and n=162 placebo. Key secondary endpoints included change from baseline in MADRS total score at Week 1 (-7.2 Auvelity vs -5.0 placebo; *P*=0.007) and remission (MADRS total score ≤10) at Week 2. The safety population was n=162 Auvelity and n=164 placebo.

†The mechanism of action of Auvelity in the treatment of MDD is unclear.

‡COMET Phase 3 safety study assessed Auvelity up to 1 year in 876 MDD patients (roll-over from prior Auvelity studies and newly enrolled).

LS=least square; MADRS=Montgomery-Åsberg Depression Rating Scale; mITT=modified intent-to-treat; NMDA=N-methyl-D-aspartate

IMPORTANT SAFETY INFORMATION (CONT'D)

CONTRAINDICATIONS

Seizure: Do not use Auvelity in patients with a seizure disorder.

Current or prior diagnosis of bulimia or anorexia nervosa: A higher incidence of seizure was observed in such patients treated with bupropion.

Undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs: Due to risk of seizure.

Monoamine Oxidase Inhibitors (MAOIs): Do not use Auvelity concomitantly with, or within 14 days of stopping, an MAOI due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome. Conversely, at least 14 days must be allowed after stopping Auvelity before starting an MAOI antidepressant. Do not use Auvelity with reversible MAOIs such as linezolid or intravenous methylene blue.

Hypersensitivity: Do not use in patients with known hypersensitivity to dextromethorphan, bupropion, or any component of Auvelity. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion. Arthralgia, myalgia, fever with rash, and other serum sickness-like symptoms suggestive of delayed hypersensitivity have also been reported with bupropion.

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors in Pediatrics and Young Adults: Monitor all antidepressant-treated patients for any indication 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 Auvelity, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Seizure: Bupropion, a component of Auvelity, can cause seizure and the risk is dose related. Because the risk of seizure with bupropion is dose-related, screen patients for use of other bupropion-containing products prior to initiating Auvelity. If concomitant use of Auvelity with other bupropion-containing products is clinically warranted, inform patients of the risk. Discontinue Auvelity and do not restart treatment if the patient experiences a seizure.

Increased Blood Pressure and Hypertension: Treatment with bupropion, a component of Auvelity, can cause elevated blood pressure and hypertension. The risk of hypertension is increased if Auvelity is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity. Assess blood pressure before initiating treatment with Auvelity and monitor periodically during treatment. Monitor blood pressure, particularly in patients who receive the combination of bupropion and are receiving nicotine replacement.

Activation of Mania/Hypomania: Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating Auvelity, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). Auvelity is not approved for use in treating bipolar depression.

Psychosis and Other Neuropsychiatric Reactions: Auvelity contains bupropion and dextromethorphan. Depressed patients treated with bupropion have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Dextromethorphan overdose can cause toxic psychosis, stupor, coma, and hyperexcitability. Because the risks of neuropsychiatric reactions are dose-related, screen patients for use of other bupropion- or dextromethorphan-containing products prior to initiating Auvelity. If concomitant use of Auvelity with other bupropion- or dextromethorphan-containing products is clinically warranted, monitor patients for neuropsychiatric reactions and instruct patients to contact a healthcare provider if such reactions occur.

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressants, including Auvelity, may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including Auvelity, in patients with untreated anatomically narrow angles.

Dizziness: Auvelity may cause dizziness. Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that Auvelity therapy does not affect them adversely.

Serotonin Syndrome: Auvelity contains dextromethorphan. Concomitant use with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants increases the risk of serotonin syndrome, a potentially life-threatening condition. Prior to initiating therapy with Auvelity, screen patients for use of other dextromethorphan-containing products. If concomitant use of Auvelity with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome, and monitor for symptoms. Discontinue Auvelity and/or concomitant serotonergic drug(s) immediately if symptoms of serotonin syndrome occur and initiate supportive symptomatic treatment.

WARNINGS AND PRECAUTIONS (CONT'D)

Embryo-fetal Toxicity: Based on animal studies, Auvelity may cause fetal harm when administered during pregnancy. Discontinue treatment in pregnant females and advise the patient about the potential risk to a fetus. Use alternative treatment for females who are planning to become pregnant.

Auvelity™
(dextromethorphan HBr and bupropion HCl)
extended-release tablets 45mg/105mg

DRUG INTERACTIONS

Strong Inhibitors of CYP2D6: Concomitant use with Auvelity increases plasma concentrations of dextromethorphan. Dosage adjustment is necessary. Monitor patients for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

Strong CYP2B6 Inducers: Concomitant use with Auvelity decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy of Auvelity. Avoid co-administration of Auvelity.

CYP2D6 Substrates: Concomitant use with Auvelity can increase the exposures of drugs that are substrates of CYP2D6. It may be necessary to decrease the dose of CYP2D6 substrates, particularly for drugs with a narrow therapeutic index.

Digoxin: Concomitant use with Auvelity may decrease plasma digoxin levels. Monitor plasma digoxin levels in patients treated concomitantly with Auvelity.

Drugs that Lower Seizure Threshold: Concomitant use with Auvelity may increase risk of seizure. Use Auvelity with caution. Discontinue Auvelity and do not restart treatment if the patient experiences a seizure.

Dopaminergic Drugs: Concomitant use with Auvelity can result in central nervous system toxicity. Use Auvelity with caution.

USE IN SPECIFIC POPULATIONS

Lactation: Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with Auvelity and for 5 days following final dose.

Renal Impairment: Dosage adjustment is recommended in patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m^2). Auvelity is not recommended in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m^2).

Hepatic Impairment: Auvelity is not recommended in patients with severe hepatic impairment.

ADVERSE REACTIONS

Most common adverse reactions (≥5% and twice the rate of placebo): dizziness (16%), headache (8%), diarrhea (7%), somnolence (7%), dry mouth (6%), sexual dysfunction (6%), and hyperhidrosis (5%).

Please see Brief Summary of Prescribing Information on the following pages, including Boxed Warning for suicidal thoughts and behaviors.

AUV HCP ISI 08/2022

References: 1. Auvelity [Prescribing Information]. Axsome Therapeutics, Inc.: New York, NY **2.** Thomas D, and Wessel C. The state of innovation in highly prevalent chronic diseases volume I: Depression therapeutics. December 2017. https://www.bio.org/sites/default/files/legacy/bioorg/docs/BIO_HPCD_Series-Depression_2018-01-03.pdf. Accessed March 21, 2022. **3.** FDA Depression Medicines. https://www.fda.gov/media/132665/download. Accessed March 21, 2022. **4.** Iosifescu DV, Jones A, O'Gorman C, et al. Efficacy and safety of AXS-05 (dextromethorphan-bupropion) in patients with major depressive disorder: A phase 3 randomized clinical trial (GEMINI). *J Clin Psychiatry*. 2022;83(4):21m14345. **5.** Data on File. AXS0080921. **6.** Tabuteau H, Jones A, Anderson A, et al. Effect of AXS-05 (dextromethorphan-bupropion) in major depressive disorder: A randomized double-blind controlled trial. *Am J Psychiatry*. 2022;179(7):490-499. **7.** Data on File. AXS0060921.

axsome®

Actor Portrayal

AUVELITY™ (dextromethorphan Hbr-bupropion HCl) extended-release tablets, for oral use

Brief Summary of Prescribing Information

BEFORE PRESCRIBING AUVELITY, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Antidepressants increased 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 emergence of suicidal thoughts and behaviors.**
- **AUVELITY is not approved for use in pediatric patients.**

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

AUVELITY is contraindicated in patients:

- with a seizure disorder
- with a current or prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with the immediate release formulation of bupropion
- undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs
- taking, or within 14 days of stopping, MAOIs due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome. Starting AUVELITY in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated.
- with known hypersensitivity to bupropion, dextromethorphan, or other components of AUVELITY. Anaphylactoid / anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion. Arthralgia, myalgia, fever with rash, and other serum sickness-like symptoms suggestive of delayed hypersensitivity have also been reported with bupropion.

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional patients
18-24 years old	5 additional patients
	Decreases Compared to Placebo
25-64 years old	1 fewer patient
≥65 years old	6 fewer patients

*AUVELITY is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication 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 AUVELITY, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Seizure

Bupropion, a component of AUVELITY, can cause seizure. The risk of seizure with bupropion is dose-related.

When a bupropion hydrochloride (HCl) sustained-release tablet was dosed up to 300 mg per day (approximately 1.5 times the maximum recommended daily dosage of AUVELITY), the incidence of seizure was approximately 0.1% (1/1,000) and increased to approximately 0.4% (4/1,000) at the maximum recommended dosage for the sustained-release tablet of 400 mg per day (approximately 2 times the maximum recommended daily dosage of AUVELITY).

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment with AUVELITY. AUVELITY is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs. The following conditions can also increase the risk of seizure: severe head injury; arteriovenous malformation; CNS tumor or CNS infection; severe stroke; concomitant use of other medications that lower the seizure threshold (e.g., other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids); metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia); use of illicit drugs (e.g., cocaine); or abuse or misuse of prescription drugs such as CNS stimulants. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic drugs or insulin; use of anorectic drugs; and excessive use of alcohol, benzodiazepines, sedative/hypnotics, or opiates.

Because the risk of seizure with bupropion is dose-related, screen patients for use of other bupropion-containing products prior to initiating AUVELITY. If concomitant use of AUVELITY with other bupropion-containing products is clinically warranted, inform patients of the risk. Discontinue AUVELITY and do not restart treatment if the patient experiences a seizure.

Increased Blood Pressure and Hypertension

AUVELITY contains bupropion, which can cause elevated blood pressure and hypertension. The risk of hypertension is increased if AUVELITY is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity. Assess blood pressure prior to initiating treatment, and periodically monitor blood pressure during treatment with AUVELITY.

Activation of Mania/Hypomania

Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating AUVELITY, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). AUVELITY is not approved for use in treating bipolar depression.

Psychosis and Other Neuropsychiatric Reactions

AUVELITY contains bupropion and dextromethorphan. Depressed patients treated with bupropion have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. Some of these patients had a diagnosis of bipolar disorder. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Dextromethorphan overdose can cause toxic psychosis, stupor, coma, and hyperexcitability.

Because the risks of neuropsychiatric reactions are dose-related, screen patients for use of other bupropion- or dextromethorphan-containing products prior to initiating AUVELITY. If concomitant use of AUVELITY with other bupropion- or dextromethorphan-containing products is clinically warranted, monitor patients for neuropsychiatric reactions and instruct patients to contact a healthcare provider if such reactions occur.

Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including bupropion, a component of AUVELITY, may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including AUVELITY, in patients with untreated anatomically narrow angles.

Dizziness

AUVELITY may cause dizziness. In controlled studies of AUVELITY, 14% of patients receiving AUVELITY and 6% of patients on placebo experienced dizziness. Take precautions to reduce the risk of falls, particularly for patients with motor impairment affecting gait or those with a history of falls. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that AUVELITY therapy does not affect them adversely.

Serotonin Syndrome

AUVELITY contains dextromethorphan. Concomitant use of AUVELITY with SSRIs or tricyclic antidepressants may cause serotonin syndrome, a potentially life-threatening condition with changes including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor.

Prior to initiating AUVELITY, screen patients for use of other dextromethorphan-containing products. If concomitant use of AUVELITY with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms. Discontinue AUVELITY and/or concomitant serotonergic drug(s) immediately if the above symptoms occur and initiate supportive symptomatic treatment.

Embryo-fetal Toxicity

Based on animal studies, AUVELITY may cause fetal harm when administered during pregnancy. In developmental toxicity studies in rats and rabbits, when a combination of dextromethorphan/quinidine was given to pregnant animals, fetal malformations (rabbits) and embryolethality were demonstrated in offspring. Neurotoxicity findings were observed in juvenile rats treated with a combination of dextromethorphan/quinidine on postnatal day (PND) 7, which corresponds to the third trimester of gestation through the first few months of life and may extend through the first three years of life in humans. The separate effect of dextromethorphan on developmental toxicity at the recommended clinical dose is unclear. Discontinue treatment in pregnant females and advise the patient about the potential risk to a fetus. Use alternative treatment for females who are planning to become pregnant.

ADVERSE REACTIONS

Clinical Trials Experience

AUVELITY was evaluated for safety in a total of 1114 patients with MDD or another indication from four studies (two 6-week studies in MDD, one 6-week study in another indication, and one long-term study in MDD and another indication). One 6-week study in MDD employed placebo as a control arm. Two 6-week studies, one in MDD and one in another indication, employed bupropion as a control arm. In the patients treated with AUVELITY in the long-term study (n=876), 597 received at least 6 months of treatment, and 110 received at least 12 months of treatment. The data below are based on the 6-week, placebo-controlled study in which either AUVELITY (n=162) or placebo (n=164) was administered twice daily to patients with MDD (Study 1).

Adverse Reactions Leading to Discontinuation
In the 6-week placebo-controlled study, 4% of patients treated with AUVELITY and 0% of placebo-treated patients discontinued participation due to adverse reactions. The adverse reaction that led to study discontinuation in ≥1% of patients treated with AUVELITY was anxiety (2%).

Most Common Adverse Reactions
In the 6-week placebo-controlled clinical study, the most common (incidence ≥5% for AUVELITY and more than twice as frequently as placebo) adverse reactions were dizziness (16%), headache (8%), diarrhea (7%), somnolence (7%), dry mouth (6%), sexual dysfunction (6%), and hyperhidrosis (5%).

Table 2: Adverse Reactions Occurring in ≥ 2% of Adult Patients with MDD Treated with AUVELITY and More Frequently than in Patients Treated with Placebo in a 6-Week Placebo-Controlled Study (Study 1)

Adverse Reaction	AUVELITY (N=162) %	Placebo (N=164) %
Dizziness	16	6
Nausea	13	9
Headache	8	4
Diarrhea	7	3
Somnolence	7	3
Dry mouth	6	2
Sexual dysfunction[a]	6	0
Hyperhidrosis	5	0
Anxiety	4	1
Constipation	4	2
Decreased appetite	4	1
Insomnia	4	2
Arthralgia	3	0
Fatigue[b]	3	2
Paraesthesia[c]	3	0
Vision blurred	3	0

[a]Sexual dysfunction includes orgasm abnormal, erectile dysfunction, libido decreased, anorgasmia
[b]Fatigue includes fatigue, lethargy
[c]Paraesthesia includes paraesthesia, hypoaesthesia

DRUG INTERACTIONS

Table 3: Clinically Important Drug Interactions with AUVELITY

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	The concomitant use of AUVELITY with MAOIs increases the risk of hypertensive crisis and serotonin syndrome.
Intervention	AUVELITY is contraindicated in patients taking MAOIs (including MAOIs such as linezolid or intravenous methylene blue) or in patients who have taken MAOIs within the preceding 14 days. Allow at least 14 days after stopping AUVELITY before starting an MAOI.
Serotonergic Drugs	
Clinical Impact	Concomitant use of AUVELITY with other serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Monitor for symptoms of serotonin syndrome when AUVELITY is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, consider discontinuation of AUVELITY and/or concomitant serotonergic drugs.
Drugs that Lower Seizure Threshold	
Clinical Impact	AUVELITY contains bupropion which can cause seizure. Co-administration with other drugs that lower seizure threshold may increase risk of seizure.
Intervention	Use caution when administering AUVELITY concomitantly with drugs that lower the seizure threshold. Discontinue AUVELITY and do not restart treatment if the patient experiences a seizure.
Strong Inhibitors of CYP2D6	
Clinical Impact	Concomitant use of AUVELITY with strong CYP2D6 inhibitors increases plasma concentrations of dextromethorphan.
Intervention	Dosage adjustment is necessary when AUVELITY is coadministered with strong inhibitors of CYP2D6. Monitor patients for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.
Strong Inducers of CYP2B6	
Clinical Impact	Concomitant use of AUVELITY with strong CYP2B6 inducers decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy of AUVELITY.
Intervention	Avoid co-administration of AUVELITY with strong inducers of CYP2B6. Consider alternatives to strong CYP2B6 inducers if needed.
Drugs Metabolized by CYP2D6	
Clinical Impact	*CYP2D6 Substrates* Coadministration of AUVELITY with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6. *Drugs that Require Metabolic Activation by CYP2D6* Drugs that require metabolic activation by CYP2D6 to be effective could have reduced efficacy when administered concomitantly with AUVELITY.
Intervention	*CYP2D6 Substrates* When used concomitantly with AUVELITY, it may be necessary to decrease the dose of CYP2D6 substrates, particularly for drugs with a narrow therapeutic index. *Drugs that Require Metabolic Activation by CYP2D6* Patients treated concomitantly with AUVELITY may require increased doses of drugs that require activation by CYP2D6 to be effective.
Digoxin	
Clinical Impact	Coadministration of AUVELITY with digoxin may decrease plasma digoxin levels.
Intervention	Monitor plasma digoxin levels in patients treated concomitantly with AUVELITY and digoxin.
Dopaminergic Drugs	
Clinical Impact	CNS toxicity was reported when bupropion was co-administered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness.
Intervention	Use caution when administering AUVELITY concomitantly with dopaminergic drugs.
Alcohol	
Clinical Impact	AUVELITY contains bupropion which can increase adverse neuropsychiatric events or reduce alcohol tolerance.
Intervention	The consumption of alcohol should be minimized or avoided during treatment with AUVELITY.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including AUVELITY, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-866-961-2388 or online at: https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/

Risk Summary
Based on animal studies, AUVELITY may cause fetal harm when administered during pregnancy. AUVELITY is not recommended during pregnancy. If a female becomes pregnant while being treated with AUVELITY, discontinue treatment and counsel the patient about the potential risk to a fetus.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks to the mother of untreated depression and potential effects on the fetus when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

Lactation

Risk Summary

Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with AUVELITY and for 5 days following final dose.

Renal Impairment

Dosage adjustment of AUVELITY is recommended in patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m^2). The pharmacokinetics of AUVELITY have not been evaluated in patients with severe renal impairment. AUVELITY is not recommended in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m^2).

Hepatic Impairment

No dose adjustment of AUVELITY is recommended in patients with mild (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). The pharmacokinetics of AUVELITY have not been evaluated in patients with severe hepatic impairment (Child-Pugh C). AUVELITY is not recommended in patients with severe hepatic impairment.

CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in patients known to be poor CYP2D6 metabolizers because these patients have higher dextromethorphan concentrations than extensive/intermediate CYP2D6 metabolizers.

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The Autism Biomarkers Consortium for Clinical Trials: Initial Evaluation of a Battery of Candidate EEG Biomarkers

Identifying successful treatments for children with autism spectrum disorder (ASD) has been hindered by the variability in types and severity of symptoms in children with ASD as well as unpredictable responses to interventions. The authors propose that neural biomarkers, which assess how the brain processes information, may help to identify subgroups of children with similar neurological functioning, which in turn could identify more specific types of treatments or guide the development of better measurement of treatment response. They test several EEG biomarkers for feasibility and validity as candidate biomarkers for understanding basic brain functioning and social processing in children with ASD.

AJP Audio and Video

In the December episode of AJP Audio, Rebecca B. Price, Ph.D., discusses her study in which a brief, noninvasive, computer-based intervention was found to efficiently extend the duration of rapid clinical response among depressed patients following a single ketamine infusion (Price et al., p. 959).

In December's video highlights, AJP Deputy Editor Danny Pine, M.D., discusses the articles "Naltrexone-Bupropion and Behavior Therapy, Alone and Combined, for Binge-Eating Disorder: Randomized Double-Blind Placebo-Controlled Trial" (Grilo et al., p. 927) and "Double-Blind, Sham-Controlled Randomized Trial Testing the Efficacy of fMRI Neurofeedback on Clinical and Cognitive Measures in Children With ADHD" (Lam et al., p. 947).

AJP CME

You can earn CME credits by reading articles in *The American Journal of Psychiatry*. Three articles in this issue form a short course that consists of reading the article and answering three multiple-choice questions with a single correct answer for up to 1 AMA PRA Category 1 Credit™ each. Credit is issued only to subscribers of the online AJP CME Course Program.

See the list below for articles in this month's issue that are the subject of a CME quiz.

In this issue
Technology and Mental Health: State of the Art for Assessment and Treatment (Harvey et al., p. 897)
Naltrexone-Bupropion and Behavior Therapy, Alone and Combined, for Binge-Eating Disorder: Randomized Double-Blind Placebo-Controlled Trial (Grilo et al., p. 927)
A Novel, Brief, Fully Automated Intervention to Extend the Antidepressant Effect of a Single Ketamine Infusion: A Randomized Clinical Trial (Price et al., p. 959)