Latuda®
(lurasidone HCl) tablets
20mg | 40mg | 60mg | 80mg | 120mg

Please see Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Look inside to learn more about an FDA-approved atypical antipsychotic

Product Monograph

INDICATIONS

LATUDA is indicated for treatment of adult and adolescent patients age 13 to 17 years with schizophrenia and in adult patients with major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate.

IMPORTANT SAFETY INFORMATION FOR LATUDA

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

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. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Suicidal Thoughts and Behaviors
Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behavior. LATUDA is not approved for use in pediatric patients with depression.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Exhibit 2070
Slayback v. Sumitomo
IPR2020-01053

IMPORTANT SAFETY INFORMATION FOR LATUDA

Contraindications: LATUDA is contraindicated in the following:

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone
- Strong CYP3A4 inhibitors (e.g., ketoconazole)
- Strong CYP3A4 inducers (e.g., rifampin)

For more information please visit us at: www.LATUDAhcp.com

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Table of Contents

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BIPOLAR DISORDER OVERVIEW

Bipolar disorder is a mental illness characterized by debilitating mood swings.[1] The lifetime prevalence estimate for bipolar disorder has been estimated to be approximately 4% to 5% of Americans over the age of 18.[2] Therefore, it is estimated that as many as 12.3 million people in the United States are affected by bipolar disorder.[2] Bipolar disorder is among the top 10 leading causes of disability in the United States.[3]

Bipolar disorder shows different patterns of illness and is suggested to be a spectrum of disorders. However, the main categories of bipolar disorder are bipolar I disorder and bipolar II disorder. The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) criteria for a diagnosis of bipolar I disorder includes a history of 1 or more major depressive episodes and at least 1 episode of mania. DSM-5 criteria for bipolar II disorder includes a history of 1 or more major depressive episodes and hypomanic episodes, without true manic episodes.[4]

Mania is defined as a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary), should be present.[4] During this period of mood disturbance and increased energy or activity, ≥3 of the following symptoms (4 if the mood is only irritable) need to be present to a significant degree and noticeable[4]:

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep (eg, feels rested after only 3 hours of sleep)
3. More talkative than usual or pressured to keep talking
4. Flight of ideas or subjective experience that thoughts are racing
5. Distractibility
6. Increase in goal-directed activity or psychomotor agitation
7. Excessive involvement in activities that have a high potential for painful consequences

In general, the mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or psychotic features are present.[4] The episode should not be attributable to the physiologic effects of a substance of abuse, medication, or other medical condition.

Hypomania is defined as a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.[4]

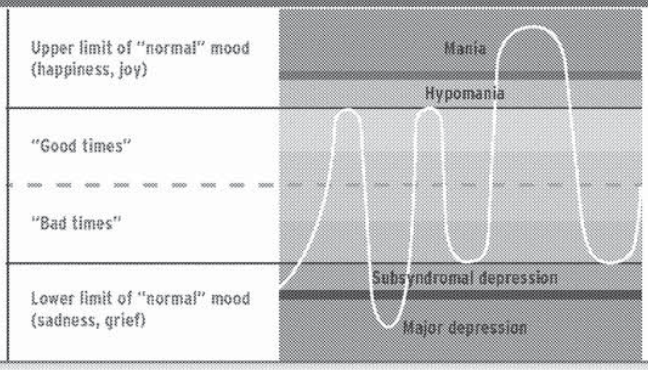
A major depressive episode is defined by the presence of ≥5 of the following symptoms during the same 2-week period, and represents a change from previous functioning. At least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
3. Significant weight loss when not dieting or weight gain
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Symptoms of a major depressive episode cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.[4] The episode should not be attributable to the physiologic effects of a substance of abuse, medication, or other medical condition.

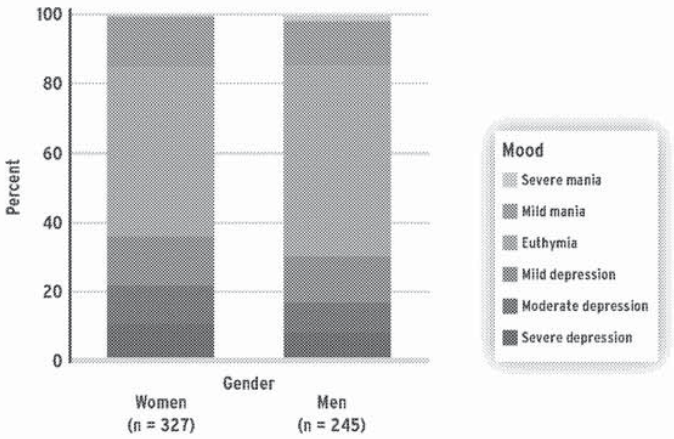
An example of a bipolar I disorder cycle is shown in Figure 1. Diagnosis of bipolar I disorder is differentiated from bipolar II disorder by determining whether there have been any past episodes of mania.

Figure 1. Representation of Mood Pattern for Bipolar I Disorder



Men and women are equally likely to develop bipolar disorder over their lifetime and the disease tends to have an onset in early adulthood.[5] Figure 2 shows the proportion of time spent ill during clinical visits for bipolar I disorder (N = 572) from one study. As for differences between genders, this study showed that women had a significantly greater number of prior depressive episodes and hospitalizations for depression.[5] Although there was no difference in time spent in mania between the 2 groups in this study, there was a trend showing that men had a greater number of lifetime hospitalizations for mania.[5]

Figure 2. Proportion of Time Spent Ill During Clinical Visits for Women and Men With Bipolar I Disorder[5]



Women (35.4%) vs men (29.3%) for depressed visits; women (49.3%) vs men (56.1%) for euthymic visits; women (15.1%) vs men (14.6%) for hypomanic or manic visits.

A common misconception about the disease course of bipolar disorder is that patients spend an equal amount of time, when ill, either manic or depressed. Contrary to this belief, a longitudinal study (approximately 13 years of follow-up) of patients with bipolar I disorder demonstrated that depressive symptoms (32% of total follow-up weeks) seem to predominate over manic/hypomanic symptoms (9% of weeks) or cycling/mixed symptoms (6% of weeks).[6] This is termed bipolar depression and refers to the depressive phase of bipolar disorder. Symptoms of bipolar depression include: extreme sadness, anxiety, fatigue, hopelessness, inactivity and disinterest in usual activities, disruptions to sleeping and eating patterns, and thoughts of death or suicide.[1] This sometimes prevents early diagnosis of bipolar disorder since, when symptomatic, most people with bipolar I disorder tend to spend about 70% of the time in the depressed state.[6]

Furthermore, monitoring for symptoms consistent with bipolar disorder is important since approximately 15% of people diagnosed with unipolar depression, and who self-report episodes consistent with mania, may be at risk for undiagnosed bipolar disorder.[7]

Bipolar Disorder Clinical and Economic Burden

Disease Burden

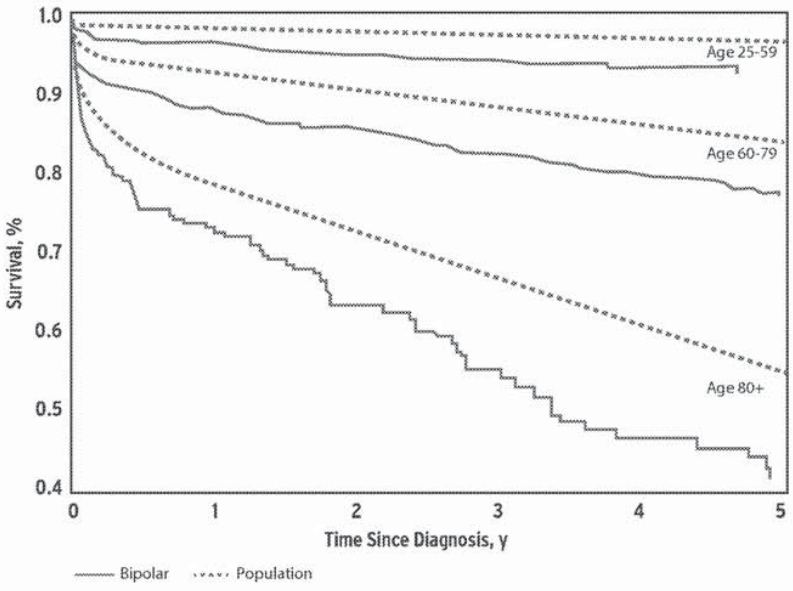
Bipolar disorder is a burdensome illness characterized by recurrent episodes of major depressive episodes and mania (or mixed episodes of the 2) or hypomania. In a longitudinal study (approximately 13 years of follow-up) of patients with bipolar I disorder (N = 146), patients were symptomatically ill nearly half of all of the weeks they were followed.[6] Additionally, patients with bipolar I disorder changed symptom status an average of 6 times per year and polarity more than 3 times per year.[6] These events take a heavy toll on a patient's health status and affect family, social, and work relationships.

Mortality Risk From General Medical Conditions and Life Expectancy

Bipolar disorder can also double a person's risk of early death from a range of medical conditions.[8] Patients with bipolar disorder have increased risk for metabolic syndrome, high blood glucose and cholesterol, high blood pressure, and obesity.[9] These factors are closely associated with the risk for cardiovascular disease (CVD).

Mortality ratios for death from general medical conditions, such as cardiovascular, respiratory, cerebrovascular, and endocrine disorders, are significantly higher among patients with bipolar disorder compared with persons with no psychiatric illness.[9] Recently, in a large population-based study of 17,101 patients with bipolar disorder it was shown that mortality from CVD was 2-fold higher in this population compared with the general population, and 38% of all deaths in persons with bipolar disorder were caused by CVD.[9] Furthermore, patients with bipolar disorder died of CVD approximately 10 years earlier than the general population and 5-year survival rates (by patient age) after first hospital admission for CVD were significantly lower among patients with bipolar disorder than individuals in the general population (Figure 3).[9]

Figure 3. Survival (5-Year) of Patients With Bipolar Disorder After Discharge From First Cardiovascular Hospital Admission[9]



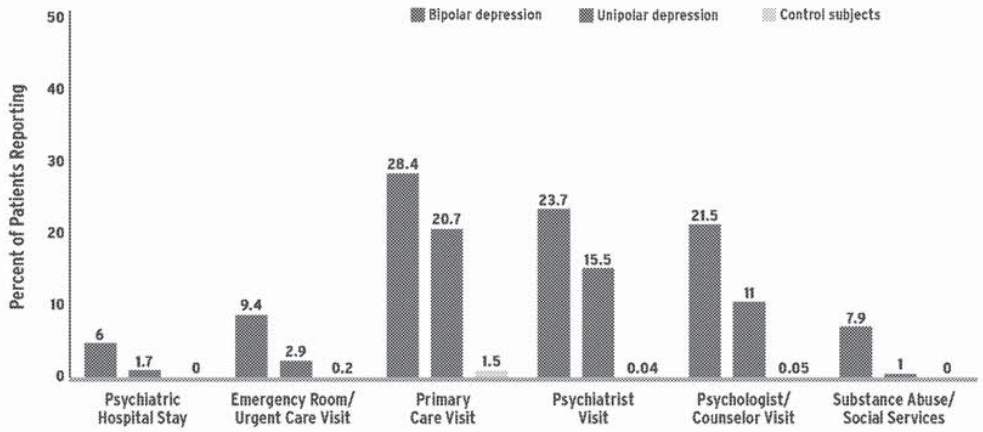
Biological factors, unhealthy lifestyle (eg, smoking and unhealthy diet), adverse medication effects, and disparities in healthcare are all possible underlying contributors to increased mortality in bipolar disorder.[8] It has been shown that life expectancy in patients with bipolar disorder is reduced by nearly 14 years in men and by 12 years in women.[10]

LATUDA has not been shown or indicated to impact mortality in prospective, randomized, placebo-controlled trials.

Economic Burden

Estimates of healthcare utilization costs for patients with bipolar disorder are 2.5 times greater than for general medical outpatients.[11] In 2002, a US population-based survey of people with bipolar depression showed higher healthcare utilization patterns over 12 months compared with people who had unipolar depression.[12] More frequent office visits, emergency care visits, hospitalizations, and use of social services were reported by patients with bipolar depression compared with patients with unipolar depression (Figure 4).[12] For example, patients with bipolar depression were twice as likely to seek counseling and 3.5 times as likely to need a psychiatric hospital stay than patients with unipolar depression.

Figure 4. Medical and Social Services Use Over 12 Months in Bipolar Depression (Bipolar Depression vs Unipolar Depression; $P<0.05$)[12]



LATUDA has not been shown or indicated to impact healthcare costs in prospective, randomized, placebo-controlled trials.

Residual Symptoms and Medication Nonadherence Are Factors Associated With the Continued Burden of Bipolar Depression

In the large Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, patients with bipolar disorder were followed for up to 2 years.[13] Two observations were made about patients who had yet to recover from their symptoms in this study. The first was that, despite appropriate clinical treatment based on available guidelines, nearly 50% of the participants experienced a recurrence of their symptoms by the end of the 2-year follow-up period.[13] The second observation was that 70% of recurrence episodes were to a depressed state and the risk for recurrent depressive episodes increased by 14% for every depressive symptom present at recovery.[13] This study confirmed that residual symptoms early in recovery predict recurrence, particularly for the depression associated with bipolar disorder.[13] In one other study, patients recovering with residual symptoms experienced a subsequent major episode approximately 3 times faster than patients recovering without residual symptoms.[14]

Treatment nonadherence in bipolar disorder is a common occurrence. A study evaluated adherence to antipsychotic therapy with aripiprazole, quetiapine, and ziprasidone in the 6 months following hospitalization of 84 patients with bipolar disorder.[15] In the 6 months following hospitalization, patients with bipolar disorder received medication enough to cover only 37% of their follow-up days.[15] Several reasons for poor adherence were discussed including symptoms of the disease itself, medication side effects, substance abuse, lack of support systems, stress, and inadequate patient-healthcare provider relationships.[15] Clinical features that have been shown to be significantly associated with poor adherence included rapid bipolar cycling, suicide attempts, earlier onset of illness, and current anxiety or alcohol use disorder ($P<0.05$).[16]

These data suggest that there is a need to appropriately treat the depressive episodes associated with bipolar disorder and to provide education to patients and their caregivers on the importance of medication adherence to maintain disease stability.

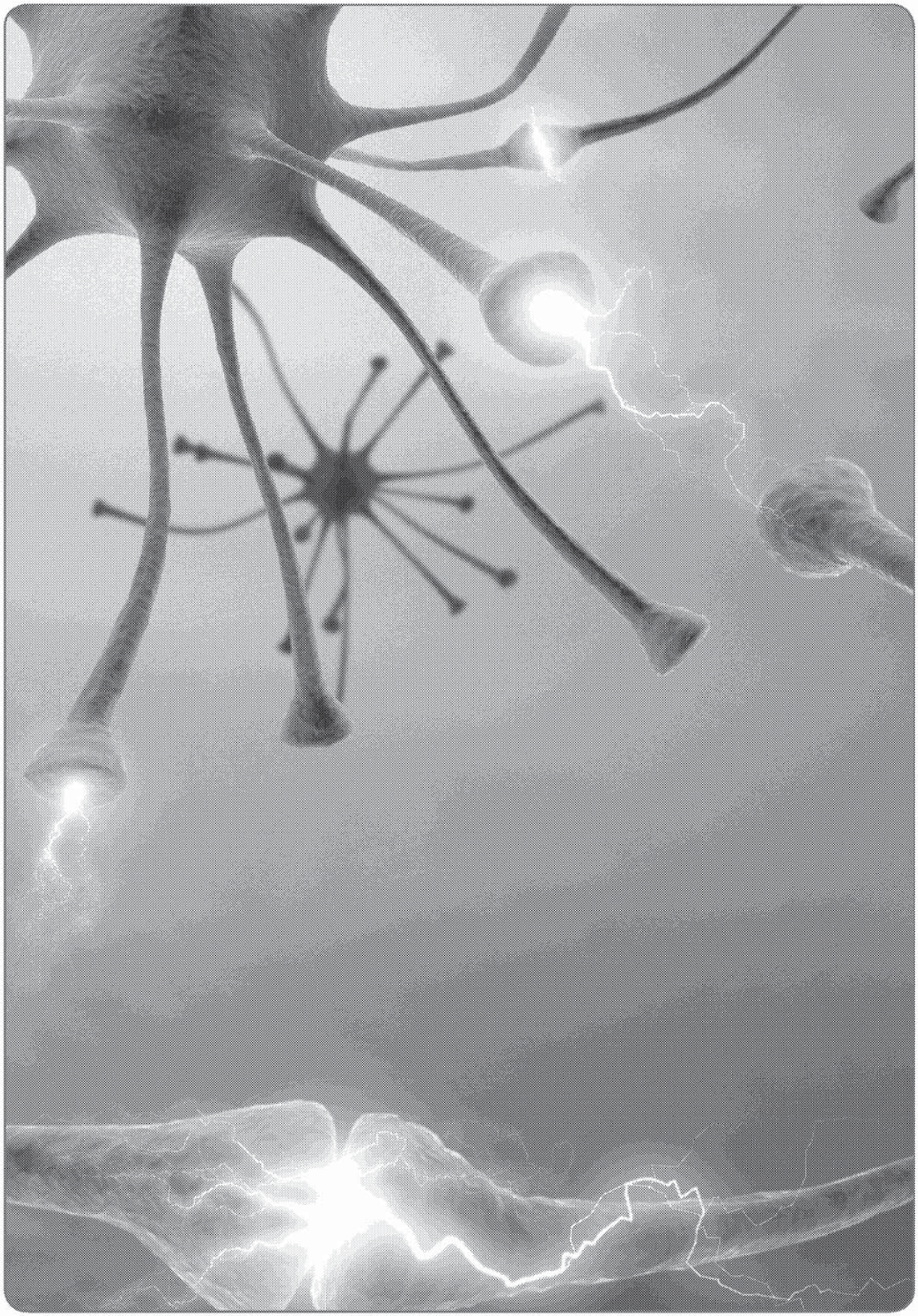
LATUDA has not been shown or indicated to impact adherence in prospective, randomized, placebo-controlled trials

Summary of Bipolar I Disorder

Bipolar I disorder is a chronic mood disorder associated with high rates of disability and medical comorbidities, premature mortality from general medical conditions, in particular CVD, and risk of suicide. Although manic episodes are a key diagnostic factor of bipolar I disorder, patients will spend a high proportion of their symptomatic days in a depressed state and these symptoms tend to recur if inadequately treated.

Furthermore, since definitive diagnosis is sometimes delayed, information from previous medical records as well as family, friends, and coworkers may aid in the more timely diagnosis of bipolar disorder. In turn, bipolar disorder is an important consideration in the differential diagnosis of major depressive disorder.

LATUDA has not been shown or indicated to impact mortality in prospective, randomized, placebo-controlled trials.



9

SCHIZOPHRENIA OVERVIEW

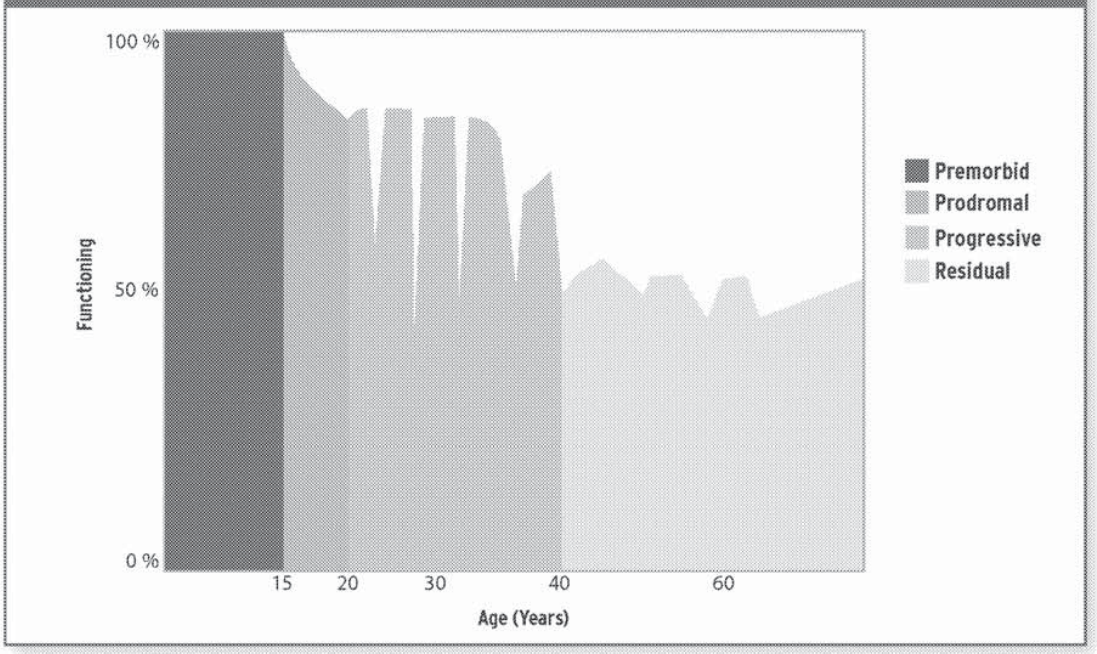
Adults

Schizophrenia is a widespread mental illness affecting more than 2 million Americans.[17,18] It affects both men and women, with symptoms typically beginning in adolescence and early adulthood.[19]

The etiology of schizophrenia is multifactorial and poorly understood.[20] Although a direct biological cause has not been determined, genetic and environmental factors appear to play a role.[20] Evidence suggests that patients with schizophrenia have multiple abnormalities in brain anatomy.[20]

Schizophrenia has 4 recognized clinical stages based on a patient's overall level of functioning: premorbid, prodromal, progressive, and residual.[20,21] The mean age range of these stages and the associated decline in functioning are presented in Figure 5.

Figure 5. Four Clinical Stages of Schizophrenia[20,21]



Adapted from Lewis DA, Lieberman JA. *Neuron*. 2000;28(2):325-334.

The characteristic symptoms of schizophrenia involve a range of cognitive, behavioral, and emotional dysfunctions, but no single symptom is pathognomonic of the disorder. The diagnosis involves the recognition of a constellation of signs and symptoms associated with impaired occupational or social functioning. Individuals with the disorder will vary substantially on most features, as schizophrenia is a heterogeneous clinical syndrome.[18] DSM-5 diagnostic criteria for schizophrenia require that two or more of the following are each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3)[18]:

1. Delusions
2. Hallucinations
3. Disorganized speech (eg, frequent derailment or incoherence)
4. Grossly disorganized or catatonic behavior
5. Negative symptoms (ie, diminished emotional expression or avolition)

Furthermore, for a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).[18] Continuous signs of the disturbance persist for at least 6 months. This 6-month

period must include at least one month of symptoms (or less if successfully treated) that meet the criteria listed above (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed above if they present in an attenuated form (eg, odd beliefs, unusual perceptual experiences).[18] Other symptoms of schizophrenia may include hostility, excitement, emotional and social withdrawal, uncooperativeness, as well as impaired attention, executive functioning, and verbal fluency.[22] Schizoaffective disorder and depressive or bipolar disorder with psychotic features should be ruled out, as well as disturbances attributable to a drug of abuse or medication, or another medical condition.[18] If there is a history of autism or communication disorder in childhood, then a diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to other required symptoms of schizophrenia, are also present for at least one month.[18]

Adolescents

Approximately one-third of individuals develop schizophrenia before the age of 18.[23] Adolescents age 13 to 17 years with schizophrenia are diagnosed according to the same criteria as adults, though it is important to note that the disorder presents differently in these younger individuals, making its recognition more difficult. Adolescent-onset schizophrenia is characterized by a more insidious onset with a relative lack of symptom specificity in the early stages of the disease, the potential for more prominent negative symptoms, frequently disorganized behavior or dysfunctional ways of thinking, and less complex delusions and hallucinations. The duration of untreated psychosis can be 3.5 times longer in patients with early-onset schizophrenia versus those with adult-onset schizophrenia.[24]

Short-term outcomes appear worse for adolescents with schizophrenia than for their adult counterparts. Over time, patients can typically expect a chronic, unremitting course with severe impairment as adults. However, this path can vary considerably in terms of impairment level and social and psychiatric support needed.[25]

Additional clinical resources are needed to assist healthcare professionals with identifying schizophrenia in adolescents. The stigma associated with the illness can delay communication of an actual diagnosis to the patient and family.[24,26] The severe and extended clinical course and poor outcomes associated with adolescent schizophrenia highlight the need for early recognition, diagnosis, and intervention.[24,25]

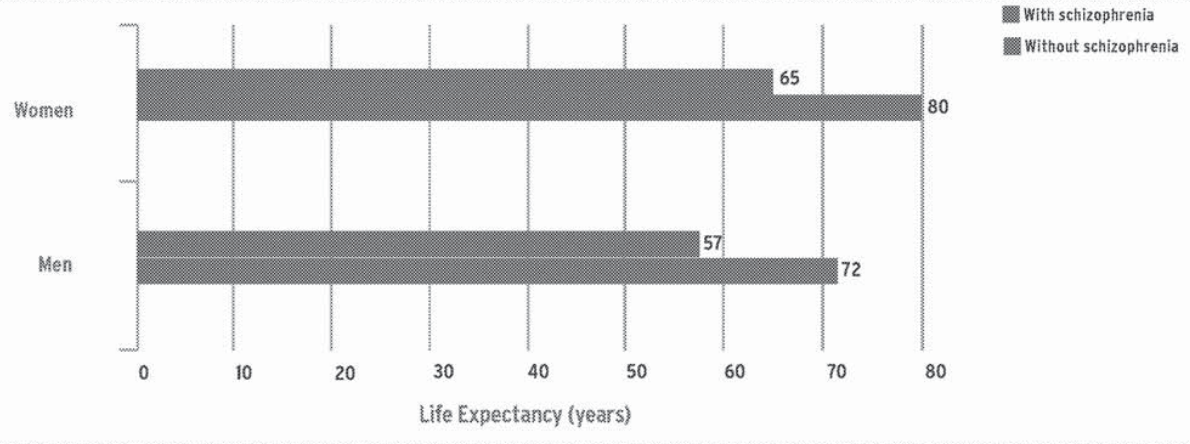
Schizophrenia Clinical and Economic Burden

Disease Burden and Life Expectancy

Although schizophrenia is a brain disorder, it has been shown to adversely affect not only mental, but also overall physical health, leading to increased morbidity and mortality.[20,27]

The life expectancy of people with mental illness is, on average, 13 to 30 years shorter than that of the general population.[27] The cause of premature mortality is largely attributed to coronary heart disease (Figure 6).[28]

Figure 6. Shorter Life Expectancy in Individuals With Schizophrenia[28]



LATUDA has not been shown or indicated to impact mortality or life expectancy in prospective, randomized, placebo-controlled trials.

Cardiovascular Risk

Coronary heart disease accounts for one-half to three-fourths of deaths in patients with schizophrenia as compared with about one-third of deaths in the general population.[28] Rates of cardiovascular risk factors, including obesity, cigarette smoking, diabetes, hypertension, dyslipidemia, and metabolic syndrome, are up to 4 times higher in patients with schizophrenia than in the general population (Table 1).[29-33]

Table 1. Cardiovascular Disease Risk Factors Associated With Schizophrenia[29-33]

Cardiovascular Risk Factors	Prevalence in General Population	Prevalence in Schizophrenia Population[29]	Relative Risk (RR)*
Obesity	34%[30]	45%-55%	1.5-2
Smoking	21%[31]	50%-80%	2-4
Diabetes	8%[31]	10%-15%	1-1.5
Hypertension	24%[31]	19%-58%	1-2
Dyslipidemia	16%[32]	25%-69%	1-4
Metabolic syndrome	34%[33]	37%-63%	1-2

*Relative risk (RR) = the risk of an event relative to exposure; value above 1 indicates increased risk.

The term "metabolic syndrome" refers to a group of abnormalities that is widely considered to be a precursor of diabetes and CVD. Metabolic syndrome can be constituted by changes in several cardiometabolic risk categories, including elevated fasting blood glucose, altered lipid profile, elevated blood pressure, being overweight or obese, and central adiposity. Patients with schizophrenia may be more susceptible to changes in these parameters than the general population and, therefore, may have a higher risk of metabolic syndrome and cardiovascular comorbidities.[34,35]

According to a meta-analysis including over 25,000 patients with schizophrenia, the rate of metabolic syndrome in these patients approached 50%, compared with 33% in the general population.[36] Additionally, atypical antipsychotic medications are associated with changes in metabolic parameters.[37,38] Other contributing factors that may affect metabolic risk in patients with schizophrenia are that they receive less frequent or no screening and fewer treatments for cardiometabolic risk factors.[39,40]

In addition to the higher prevalence of CVD, schizophrenia is often associated with higher rates of comorbid mental illnesses as well as respiratory and infectious diseases.[41,42]

Economic Burden

Onset of symptoms of schizophrenia frequently occurs during the most productive years of adulthood (males: late teens to early 20s; females: 20s to early 30s). Therefore, the disease can lead to substantial losses in productivity and increased costs to both the patient and society.[20,43]

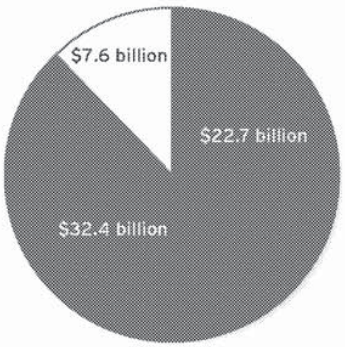
Schizophrenia has been shown to have a substantial economic impact. In a 2005 study, overall spending on schizophrenia was estimated at $62.7 billion a year (2002 data; Figure 7).[44]

Indirect costs (losses resulting from decreased productivity) made up the largest portion of spending, amounting to an estimated total of $32.4 billion. Of these, unemployment was the greatest cost, followed by caregiver expenses, reduced productivity, and suicide.[44]

Direct healthcare-related costs, including long-term care, outpatient and inpatient care, and pharmacy expenses, accounted for the second largest proportion of spending, estimated at $22.7 billion.[44] Direct non-healthcare costs, including law enforcement, homeless shelters, and research and training, accounted for an estimated $7.6 billion.[44]

LATUDA has not been shown or indicated to impact healthcare costs in prospective, randomized, placebo-controlled trials.

Figure 7. Overall Estimated Cost Associated With Schizophrenia in 2002: $62.7 Billion[44]



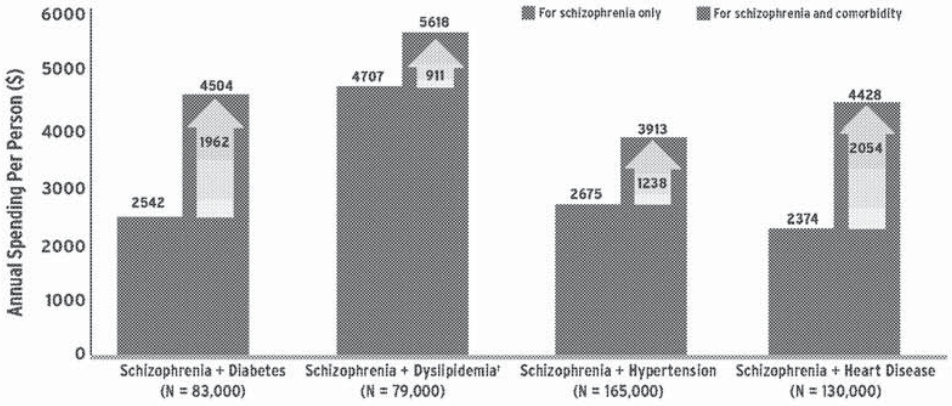
Direct Healthcare Costs: Total $22.7 Billion

	Cost	Percentage
Long-term care	$7.97	35%
Outpatient care	$6.95	31%
Pharmacy cost	$5.04	22%
Inpatient care	$2.76	12%

Direct Healthcare Costs
Indirect Costs
Direct Non-Healthcare Costs

About two-thirds of patients with schizophrenia also suffer from diabetes, dyslipidemia, hypertension, and/or heart disease, adding substantially to the economic burden of their mental illness (Figure 8).[45] Approximately 2 of 3 patients with schizophrenia have at least 1 of 4 associated comorbidities.

Figure 8. Annual Spending Per Person With Schizophrenia by Comorbidity* (2001-2002)[45]



Note: Persons with >1 comorbidity appear in multiple categories and their expenses are double counted.

*Comorbid categories are limited to diabetes, dyslipidemia, hypertension, and heart disease.

†Costs of persons with dyslipidemia should be treated with caution because relative standard error (SE) is >30%.

Factors Associated With Clinical and Economic Burden

Two factors that often play a substantial role in the high clinical and economic costs associated with schizophrenia are hospitalization and treatment nonadherence.[46-48]

A study of medical and pharmacy claims for the years 1998 to 2007 found that newly diagnosed patients (≤1 year since diagnosis) had significantly higher medical expenses in their first year of treatment than those diagnosed for 3 or more years.[46] Newly diagnosed patients were hospitalized twice as often (22.3% vs 12.4%; $P<0.0001$), spent an average of 2 more days in the hospital, and cost approximately $5000 more than chronic patients.[46]

Nonadherence to treatment is an important contributor to relapse that increases the healthcare burden of schizophrenia. One study found that continuous treatment reduced the risk of relapse by about 70%.[47]

A study of 213 patients found that discontinuation of antipsychotic medication doubled the risk of rehospitalization within the first 3 months of hospital discharge.[48]

Patient-related, treatment-related, and environmental factors may all play a contributing role in the nonadherence of patients with schizophrenia (Table 2).[20]

Table 2. Factors Contributing to Nonadherence in Patients With Schizophrenia[20]

Treatment-Related Factors	Patient-Related Factors	Environmental Psychosocial Factors
Lack of efficacy	Lack of insight about illness severity	Breakdown of therapeutic alliance
Side effects	Misconceptions about the importance of treatment	Lack of family support

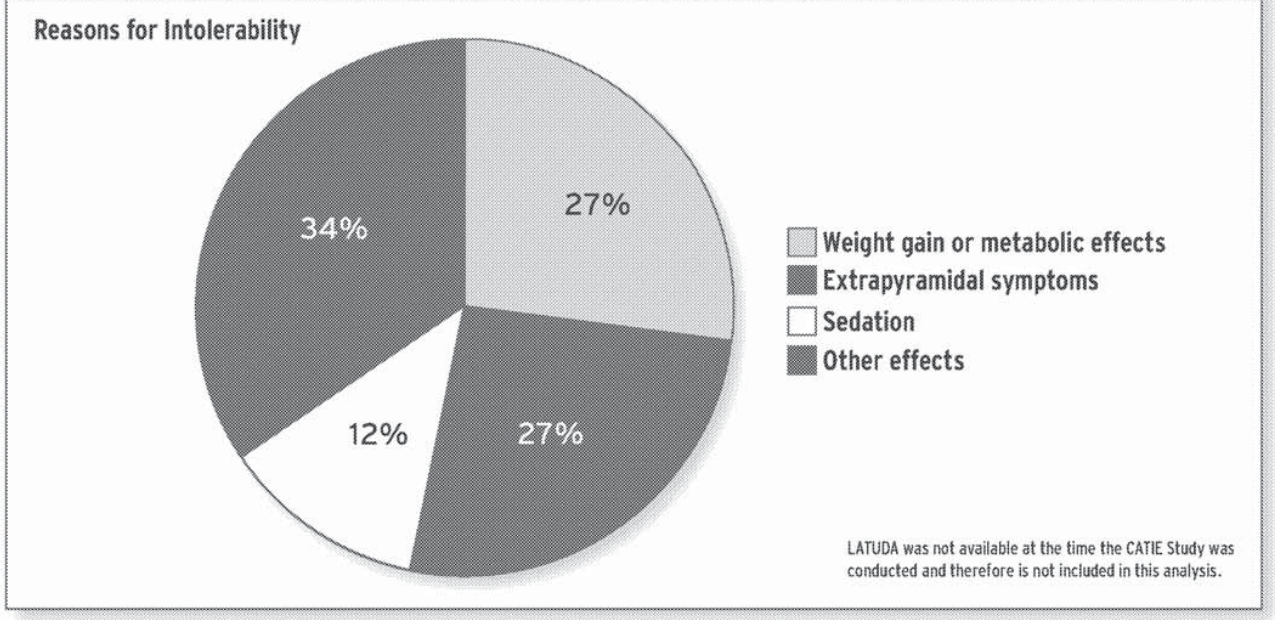
LATUDA has not been shown or indicated to impact hospitalization rates or treatment adherence in prospective, randomized, placebo-controlled trials.

Continuing Need for Additional Antipsychotics

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study compared the relative effectiveness of one first-generation (typical) antipsychotic (perphenazine) and 4 second-generation (atypical) antipsychotics (olanzapine, quetiapine, risperidone, and ziprasidone) for treatment of patients with schizophrenia.[49]

The CATIE Study indicated that 74% (1061/1432) of patients discontinued antipsychotic treatment before the 18-month study endpoint. Analysis of the reasons for discontinuation indicated that over one-half of patients discontinued treatment due to either lack of efficacy (32%) or being unable to tolerate the prescribed drug (20%).[49] The reasons given for treatment intolerance are described in Figure 9.

Figure 9. Reasons Given for Intolerance to Antipsychotic Treatment in the CATIE Study[49]



These data indicate a continuous unmet need for additional antipsychotics.

Considerations When Choosing an Antipsychotic for Schizophrenia

Having a variety of available antipsychotic drugs allows for individualization of therapy for adult patients with schizophrenia. Important considerations when choosing the appropriate antipsychotic for each patient include the patient's past responses to treatment, medication side-effect profiles, patient preferences, route of administration, presence of comorbid medical conditions, and potential interactions with other prescribed medications.[50]

Summary of Schizophrenia

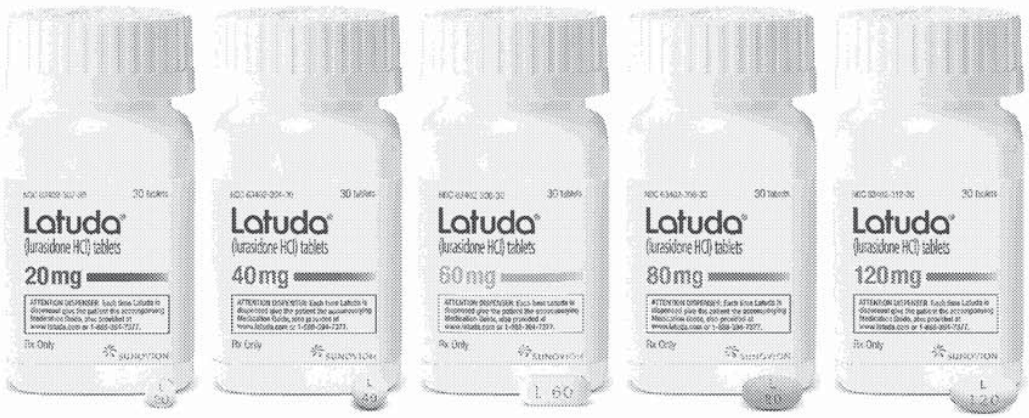
Schizophrenia is a serious chronic and disabling mental illness with a substantial clinical burden that includes poor overall physical health and higher rates of comorbid mental illnesses as well as cardiovascular, respiratory, and infectious diseases; all of which can contribute to a reduced life expectancy.[19,20,27,28]

Schizophrenia is associated with significant costs due to lost productivity and other direct and indirect healthcare- and non-healthcare-related expenses.[43,44]

Treatment nonadherence can result in poorer outcomes and may contribute to increased medical costs. Lack of treatment efficacy and/or poor tolerability and patient and environmental factors may also all contribute to nonadherence.[49]

Adolescents age 13 to 17 are diagnosed with the same criteria as adults, but schizophrenia can be harder to recognize in this population.[24] The clinical severity, impact on development, and poor prognosis of adolescent schizophrenia underscore the importance of early detection, prompt diagnosis, and effective treatment.[25]

LATUDA has not been shown or indicated to impact adherence or healthcare costs in prospective, randomized, placebo-controlled trials.



Tablet images shown are not actual size.

LATUDA PRODUCT PROFILE

INDICATIONS[51]

LATUDA is indicated for treatment of adult and adolescent patients age 13 to 17 years with schizophrenia and in adult patients with major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Dosage and Administration[51]

Depressive Episodes Associated With Bipolar I Disorder: The recommended starting dose of LATUDA is 20 mg given once daily as monotherapy or as adjunctive therapy with lithium or valproate. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 20 mg/day to 120 mg/day as monotherapy or as adjunctive therapy with lithium or valproate. The maximum recommended dose, as monotherapy or as adjunctive therapy with lithium or valproate, is 120 mg/day. In the monotherapy study, the higher dose range (80-120 mg/day) did not provide additional efficacy on average, compared to the lower dose range (20-60 mg/day).

Schizophrenia:

Adults

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg/day to 160 mg/day. The maximum recommended dose is 160 mg/day.

Adolescents

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg/day to 80 mg/day. The maximum recommended dose is 80 mg/day.

Administration Instructions: LATUDA should be taken with food (at least 350 calories). Administration with food substantially increases the absorption of LATUDA. Administration with food increases the AUC approximately 2-fold and increases the C_{max} approximately 3-fold. In the clinical studies, LATUDA was administered with food.

Dose Modifications in Special Populations: Dose adjustment is recommended in moderate (creatinine clearance: 30 to <50 mL/min) and severe renal impairment (creatinine clearance <30 mL/min) patients. The recommended starting dose is 20 mg/day. The dose in these patients should not exceed 80 mg/day.

Dose adjustment is recommended in moderate (Child-Pugh Score = 7 to 9) and severe hepatic impairment (Child-Pugh Score = 10 to 15) patients. The recommended starting dose is 20 mg/day. The dose in moderate hepatic impairment patients should not exceed 80 mg/day and the dose in severe hepatic impairment patients should not exceed 40 mg/day.

Dose Modifications Due to Drug Interactions: LATUDA should not be used concomitantly with a strong CYP3A4 inhibitor (eg, ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc). If LATUDA is being prescribed and a moderate CYP3A4 inhibitor (eg, diltiazem, atazanavir, erythromycin, fluconazole, verapamil, etc) is added to the therapy, the LATUDA dose should be reduced to half of the original dose level. Similarly, if a moderate CYP3A4 inhibitor is being prescribed and LATUDA is added to the therapy, the recommended starting dose of LATUDA is 20 mg/day, and the maximum recommended dose of LATUDA is 80 mg/day.

LATUDA should not be used concomitantly with a strong CYP3A4 inducer (eg, rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc). If LATUDA is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the LATUDA dose after chronic treatment (7 days or more) with the CYP3A4 inducer.

Grapefruit and grapefruit juice should be avoided in patients taking LATUDA, since these may inhibit CYP3A4 and alter LATUDA concentrations.

Availability: 20 mg, 40 mg, 60 mg, 80 mg, and 120 mg tablets.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

IMPORTANT SAFETY INFORMATION FOR LATUDA

Cerebrovascular Adverse Reactions, Including Stroke: In clinical trials, elderly subjects with dementia randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Latuda® (lurasidone HCl) tablets
20mg | 40mg | 60mg | 80mg | 120mg

Clinical Pharmacology

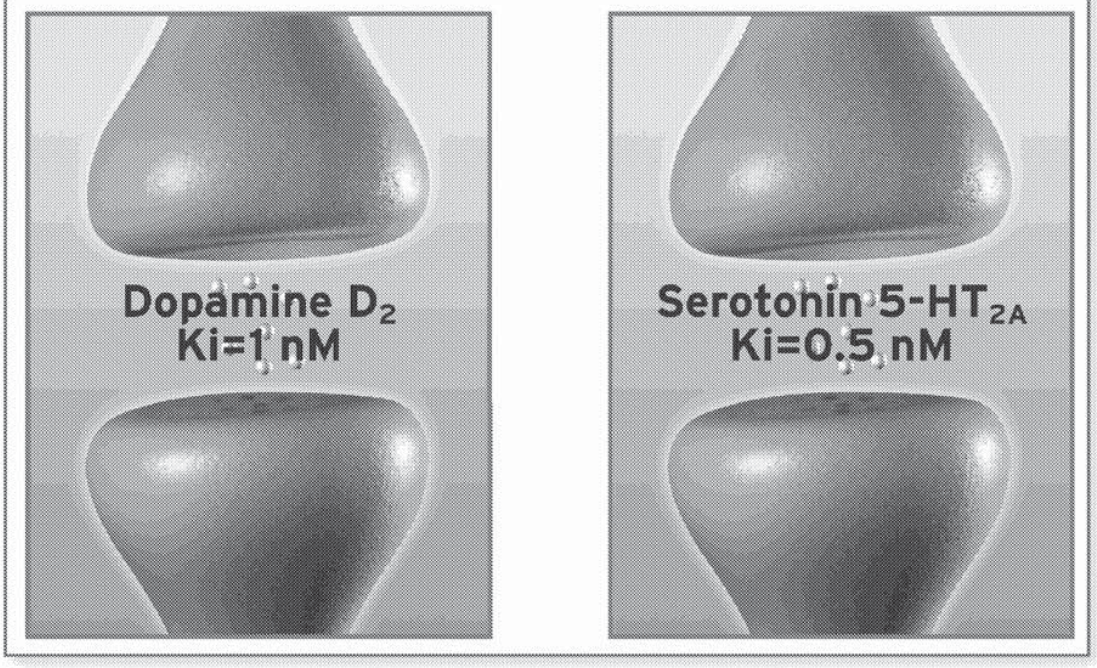
Proposed Mechanism of Action

The mechanism of action of LATUDA in the treatment of schizophrenia and bipolar depression is unknown. However, its efficacy in schizophrenia and bipolar depression could be mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 (5-HT_{2A}) receptor antagonism.[51]

In Vitro Receptor Binding

LATUDA is an antagonist with high-affinity binding at the dopamine D_2 receptors (Ki = 1 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors 5-HT_{2A} (Ki = 0.5 nM) and 5-HT_7 (Ki = 0.5 nM) (Figure 10).[51-53]

Figure 10. In Vitro Receptor Binding Affinities* of Lurasidone for D_2 and 5-HT_{2A} Receptors



*The lower the Ki value, the higher the binding affinity; the higher the Ki value, the lower the binding affinity.

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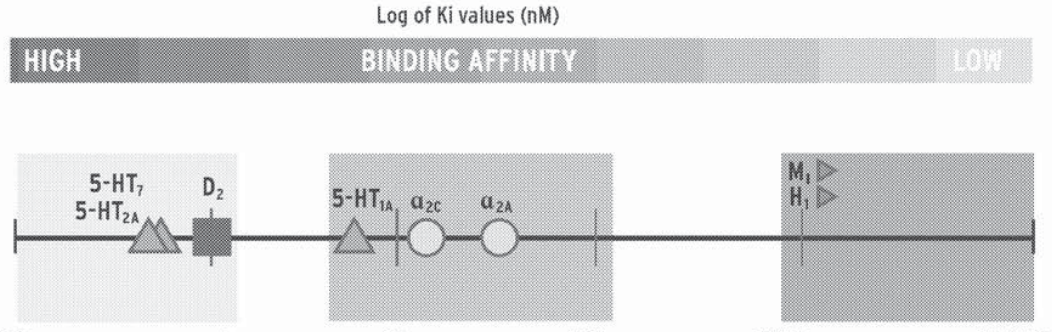
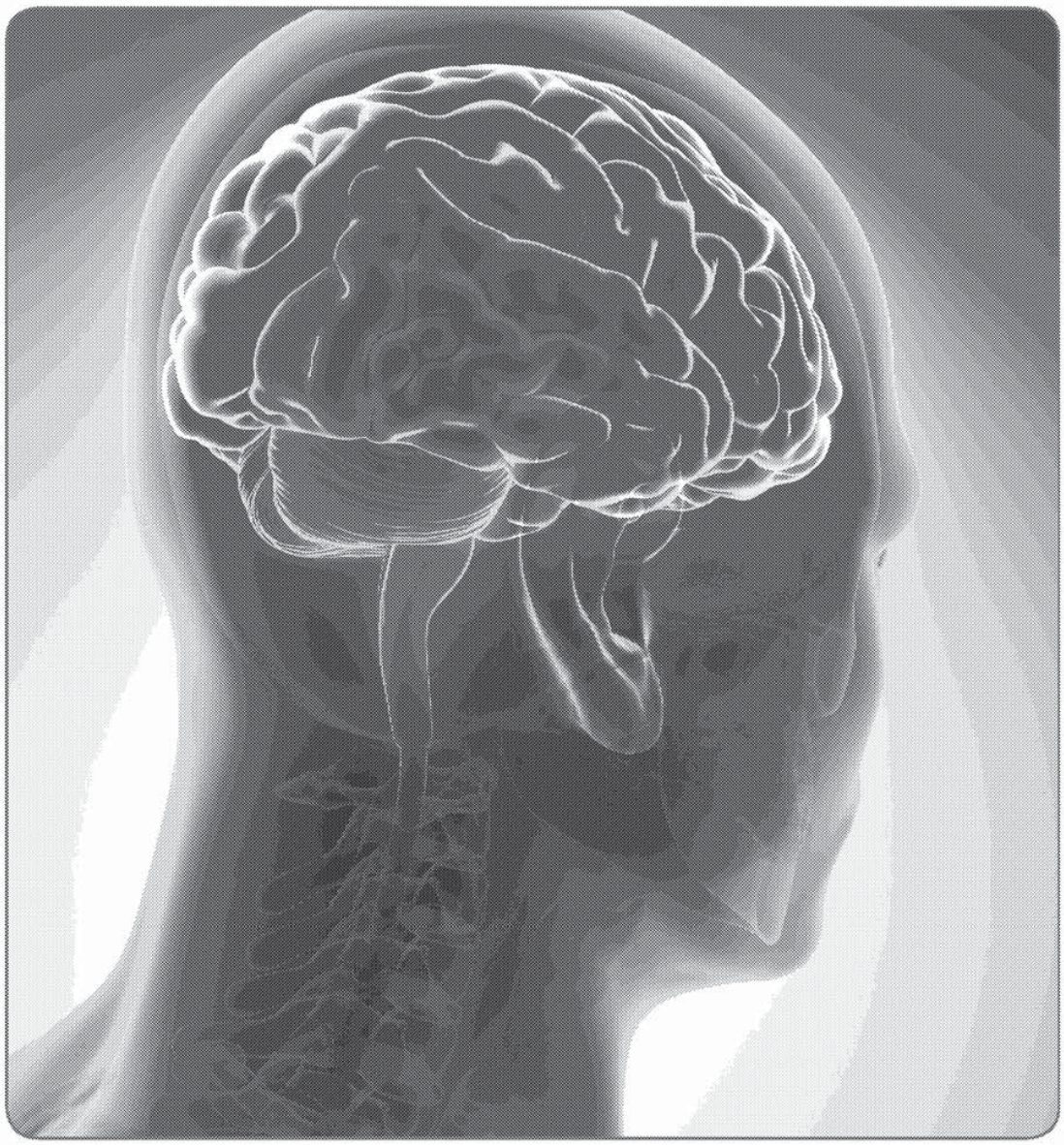
Lurasidone also binds with moderate affinity to the human α_{2C} adrenergic receptors (Ki = 11 nM), is a partial agonist at serotonin 5-HT_{1A} (Ki = 6.4 nM) receptors, and is an antagonist at the α_{2A} adrenergic receptors (Ki = 41 nM). LATUDA exhibits little or no affinity for histamine H_1 and muscarinic M_1 receptors (IC_{50} >1000 nM) (Figure 11).[51-53]

The correlation between receptor-binding affinities and clinical outcomes is uncertain.

Figure 11. In Vitro Receptor-Binding Results[51,53]



HIGH AFFINITY		MODERATE AFFINITY		LITTLE OR NO AFFINITY
Dopamine D_2	Antagonist	Adrenergic α_{2C}	Antagonist	Muscarinic M_1 IC_{50} >1000 nM
Serotonin 5-HT_{2A}	Antagonist	Serotonin 5-HT_{1A}	Partial agonist	Histamine H_1 IC_{50} >1000 nM
Serotonin 5-HT_7	Antagonist	Adrenergic α_{2A}	Antagonist	



LATUDA Efficacy

Major Depressive Episodes Associated With Bipolar I Disorder (Bipolar Depression)

The efficacy of LATUDA, as monotherapy, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (mean age of 41.5 years, range 18 to 75) who met *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision (DSM-IV-TR) criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N = 485). Patients were randomized to 1 of 2 flexible-dose ranges of LATUDA (20 to 60 mg/day, or 80 to 120 mg/day) or placebo.

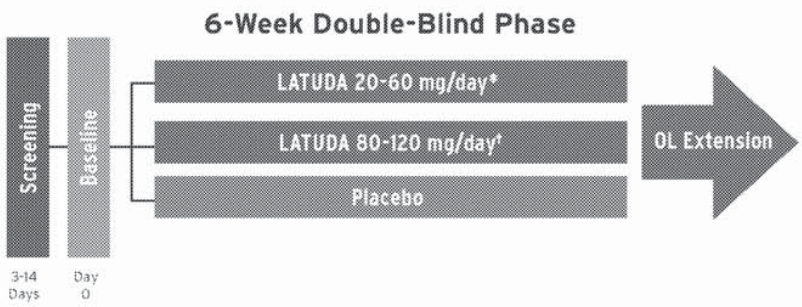
As an adjunctive therapy with lithium or valproate, the efficacy of LATUDA was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (mean age of 41.7 years, range 18 to 75) who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N = 340). Patients who remained symptomatic after treatment with lithium or valproate were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Monotherapy Study

The efficacy of LATUDA, as monotherapy, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (age range 18-75 years; N = 485) who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, without psychotic features, and with a history of at least one lifetime bipolar manic or mixed manic episode. Eligible adult outpatients were randomized (1:1:1) to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo (Figure 12).[54]

Figure 12. Design of the Monotherapy Study[54]



*Started at 20 mg/day for 7 days, then flexible dosing.

†Started at 20 mg/day, then increased by 20 mg/day every 2 days until 80 mg/day, then flexible dosing.

Abbreviation: OL, open-label.

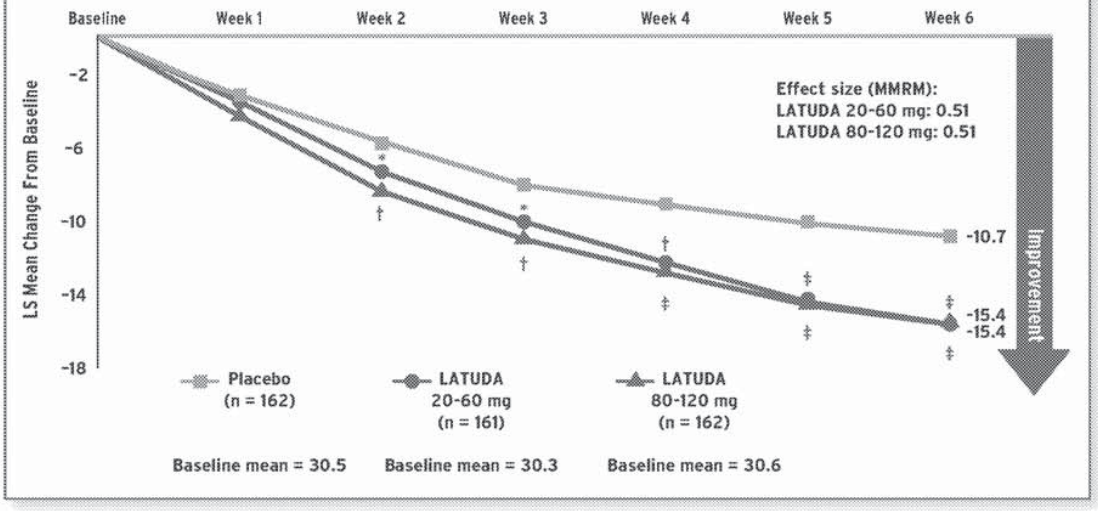
The primary endpoint of the monotherapy study was the change from baseline to Week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. The MADRS is a 10-item clinician-rated scale with total scores ranging from 0 (no depressive features) to 60 (maximum score). The key secondary endpoint was change from baseline to Week 6 in the Clinical Global Impression-Bipolar-Severity of Illness scale (CGI-BP-S) score (depression), a clinician-rated scale that measures the patient's current illness state on a 7-point scale, where a higher score is associated with greater illness severity. Other secondary endpoints and safety outcomes were also evaluated.

The primary analysis was based on the intent-to-treat (ITT) population, which included all patients who were randomized, received at least 1 dose of study medication, and had a baseline and at least 1 post-baseline efficacy measure. The primary endpoint was analyzed using a mixed model for repeated measures (MMRM). Other efficacy endpoints were analyzed using either MMRM or analysis of covariance (ANCOVA), last observation carried forward (ANCOVA-LOCF), or logistic regression. Safety analyses were based on outcomes in the safety population, which included all patients who were randomized and received at least 1 dose of study medication.

Efficacy of LATUDA as Monotherapy for Bipolar Depression

For the primary efficacy endpoint, treatment with LATUDA resulted in significantly greater MADRS score reductions at Week 6 (ITT population; N = 485) for both the 20-60 mg/day group (-15.4; $P<0.001$; effect size = 0.51) and the 80-120 mg/day group (-15.4; $P<0.001$; effect size = 0.51) versus placebo (-10.7) (Figure 13).[54] Statistically significant reductions in MADRS scores were observed in both LATUDA groups versus placebo from Week 2 onward.

Figure 13. Change From Baseline to Week 6 in MADRS Total Score in the Monotherapy Study (MMRM)[54]



*$P<0.05$; †$P<0.01$; ‡$P<0.001$.

Scale range: 0-60.

Abbreviations: LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures.

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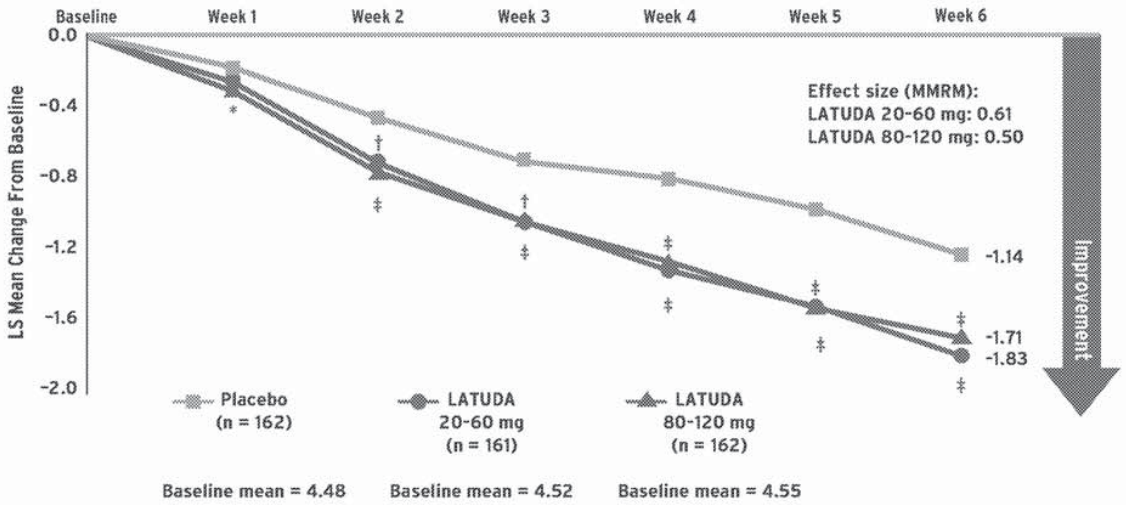
There was a significant reduction in the key secondary endpoint of change in mean CGI-BP-S score from baseline for both the LATUDA 20-60 mg/day (-1.83; *P*<0.001; effect size = 0.61) and the LATUDA 80-120 mg/day group (-1.71; *P*<0.001; effect size = 0.50) versus placebo (-1.14) at Week 6.[54] Statistically significant reductions in CGI-BP-S were observed in the LATUDA 80-120 mg/day group versus placebo from Week 1 onward (Figure 14).[54] Both LATUDA groups showed significant reductions from Week 2 onward.

Figure 14. Change From Baseline to Week 6 in CGI-BP-S Score in the Monotherapy Study (MMRM)[54]



*P<0.05; †P<0.01; ‡P<0.001.

Scale range: 1-7.

Abbreviations: CGI-BP-S, Clinical Global Impression-Bipolar-Severity of Illness scale; LS, least squares; MMRM, mixed model for repeated measures.

IMPORTANT SAFETY INFORMATION FOR LATUDA

Metabolic Changes: Atypical antipsychotic drugs have caused metabolic changes including:

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

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

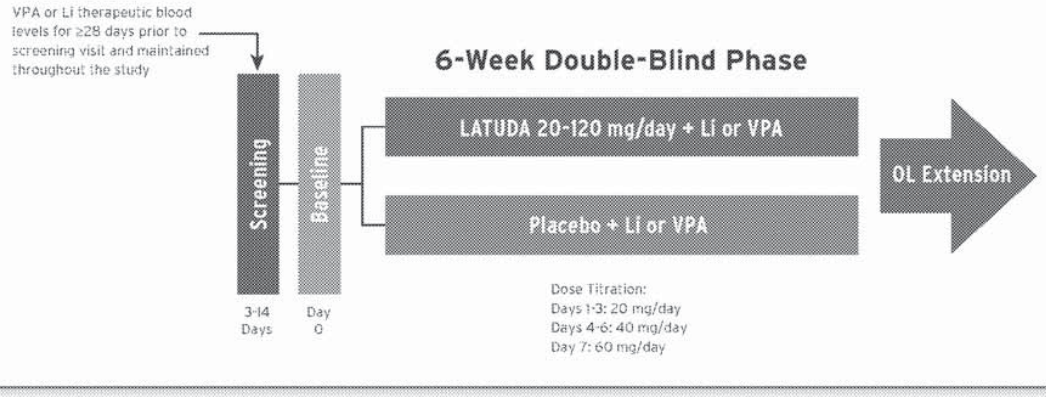
Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Latuda®
(lurasidone HCl) tablets
20mg | 40mg | 60mg | 80mg | 120mg

Adjunctive Study With Lithium or Valproate

The efficacy of LATUDA, as an adjunctive therapy with lithium or valproate, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of LATUDA for the treatment of adult patients (age range 18-75 years; N = 340) who met DSM-IV-TR criteria for depressive episodes associated with bipolar I disorder, with or without rapid cycling, without psychotic features, and with a history of at least one lifetime bipolar manic or mixed manic episode. Patients who remained symptomatic after treatment with lithium or valproate were randomized (1:1) to flexibly dosed LATUDA 20 to 120 mg/day or placebo, both adjunctive to either lithium or valproate (Figure 15).[55]

Figure 15. Design of the Adjunctive Therapy Study[55]



Abbreviations: Li, lithium; OL, open-label; VPA, valproate.

The primary endpoint of the adjunctive therapy study was the change from baseline to Week 6 in MADRS total score. The key secondary endpoint was change from baseline to Week 6 in CGI-BP-S score (depression). Other secondary endpoints and safety outcomes were also evaluated.

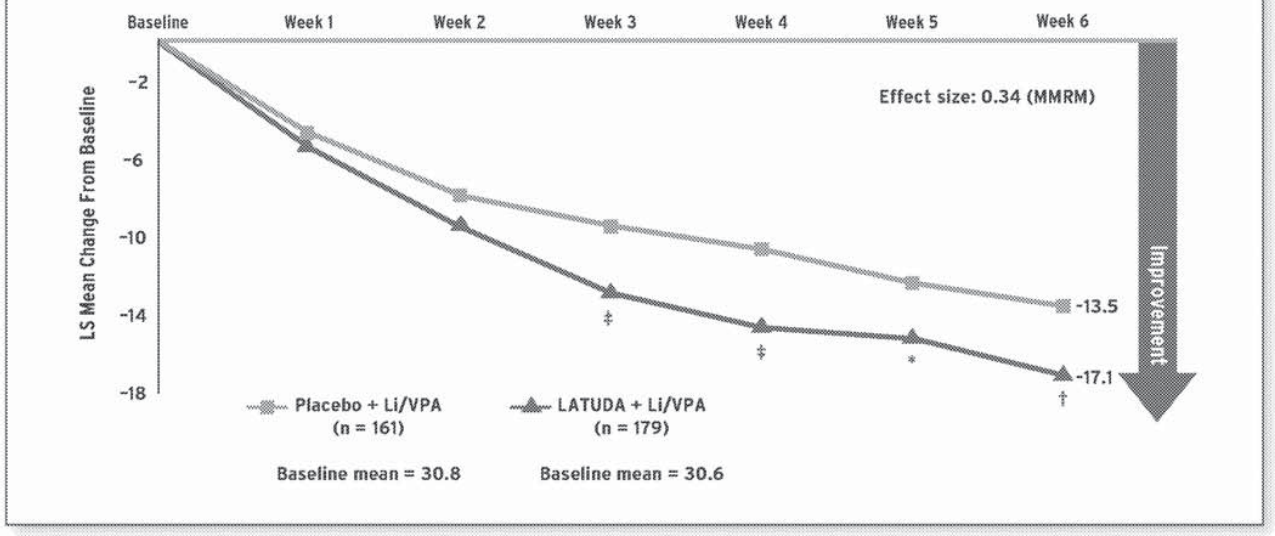
The primary analysis was based on the ITT population, which included all patients who were randomized, received at least 1 dose of study medication, and had a baseline and at least 1 post-baseline efficacy measure. Efficacy endpoints were analyzed using either MMRM or ANCOVA-LOCF, or logistic regression. Safety analyses were based on outcomes in the safety population, which included all patients who were randomized and received at least 1 dose of study medication.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Efficacy of LATUDA as Adjunctive Therapy With Lithium or Valproate for Bipolar Depression

LATUDA + lithium/valproate (Li/VPA) treatment was associated with a statistically significant greater reduction in the mean (SE) MADRS total score vs placebo + Li/VPA (-17.1 [0.87] vs -13.5 [0.91]; *P*=0.005; effect size = 0.34) at Week 3 through study endpoint (Figure 16).[55]

Figure 16. Change From Baseline to Week 6 in MADRS Total Score in the Adjunctive Therapy Study (MMRM)[55]



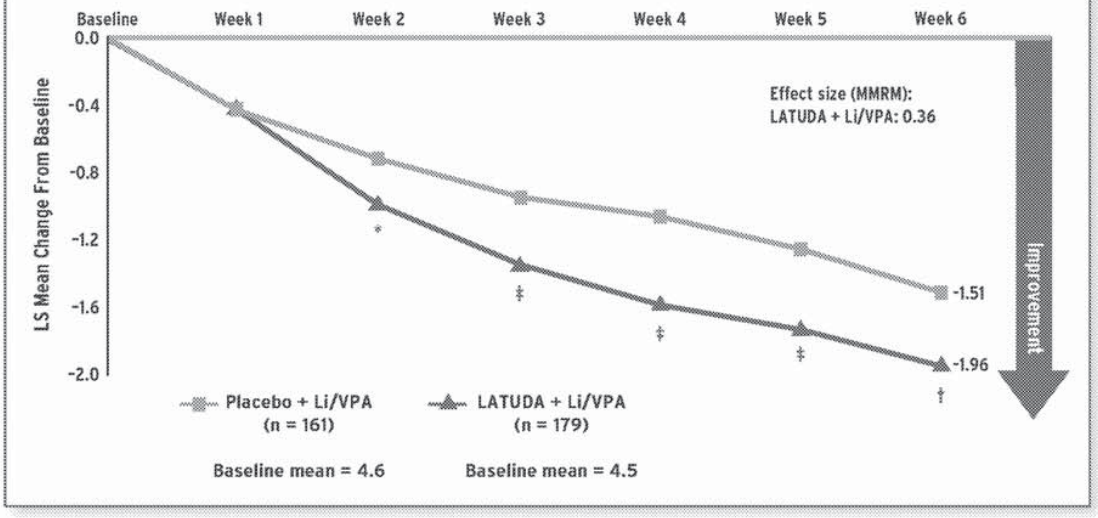
*P<0.05; †P<0.01; ‡P<0.001.

Scale range: 1-60.

Abbreviations: Li, lithium; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures; VPA, valproate.

LATUDA + Li/VPA treatment was associated with a statistically significant reduction in the mean CGI-BP-S total score versus placebo + Li/VPA (-1.96 vs -1.51, respectively, *P*=0.003; effect size = 0.36). This reduction was observed from Week 2 through study endpoint (Figure 17).[55]

Figure 17. Change From Baseline to Week 6 in CGI-BP-S Score in the Adjunctive Therapy Study (MMRM)[55]



*$P<0.05$; †$P<0.01$; ‡$P<0.001$.

Scale range: 1-7.

Abbreviations: CGI-BP-S, Clinical Global Impression-Bipolar-Severity of Illness scale; Li, lithium; LS, least squares; MMRM, mixed model for repeated measures; VPA, valproate.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

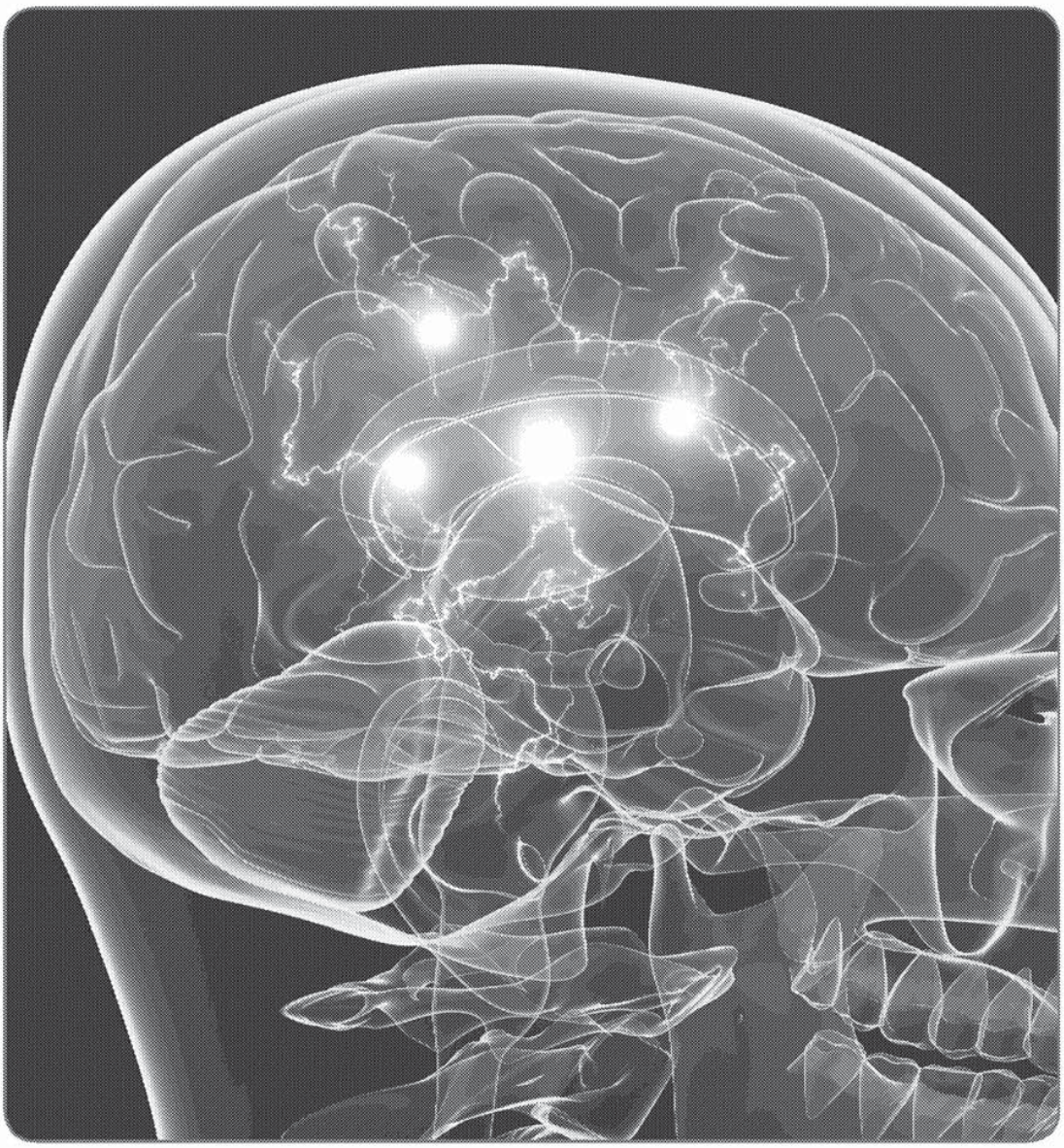
LATUDA Efficacy Summary in Bipolar Depression

Table 3. Primary Efficacy Results for Studies in Depressive Episodes Associated With Bipolar I Disorder (MADRS Scores)[51]

Study	Treatment Group	Primary Efficacy Measure: MADRS		
		Mean Baseline Score (SD)	LS Mean Change From Baseline (SE)	Placebo-Subtracted Difference[a] (95% CI)
Monotherapy Study	LATUDA (20-60 mg/day)*	30.3 (5.0)	-15.4 (0.8)	-4.6 (-6.9, -2.3)
	LATUDA (80-120 mg/day)*	30.6 (4.9)	-15.4 (0.8)	-4.6 (-6.9, -2.3)
	Placebo	30.5 (5.0)	-10.7 (0.8)	--
Adjunctive Therapy Study	LATUDA (20-120 mg/day)* + lithium or valproate	30.6 (5.3)	-17.1 (0.9)	-3.6 (-6.0, -1.1)
	Placebo + lithium or valproate	30.8 (4.8)	-13.5 (0.9)	--

Abbreviations: SD, standard deviation; SE, standard error; LS, least-squares; CI, confidence interval, unadjusted for multiple comparisons; MADRS, Montgomery-Åsberg Depression Rating Scale.

[a] Difference (drug minus placebo) in least-squares mean change from baseline. * Treatment group statistically superior to placebo.



Schizophrenia

Adults

The efficacy of LATUDA for the treatment of schizophrenia was established in 5 short-term (6-week), placebo-controlled studies in adult patients (mean age, 38.4 years; range 18-72) who met DSM-IV-TR criteria for schizophrenia. Two studies included an active-control arm (olanzapine or quetiapine extended release [XR]) to assess assay sensitivity; however, the studies were not designed for comparison of LATUDA with the active controls.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

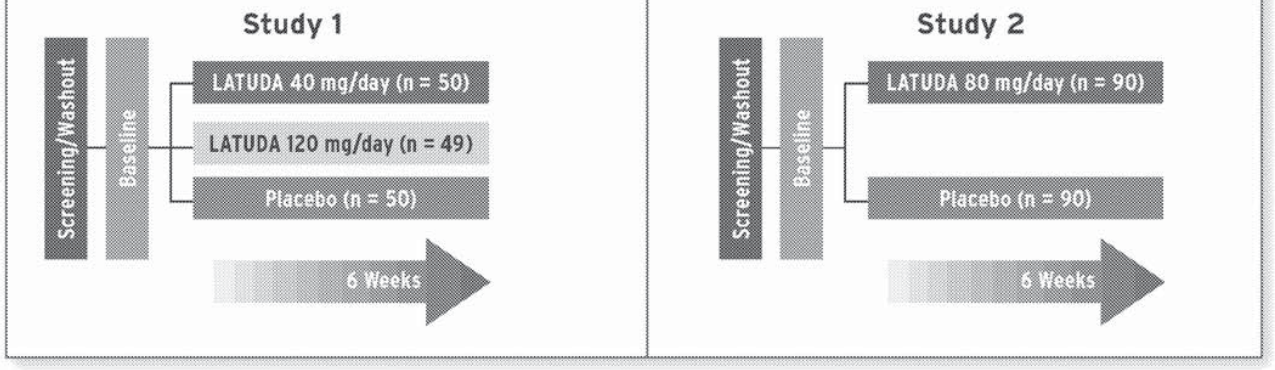
Studies 1 and 2

Study 1 (Ogasa M, et al; 2013) was a 6-week, placebo-controlled trial (N = 145) designed to evaluate the efficacy and safety of 2 fixed once-daily doses of LATUDA (40 mg/day, 120 mg/day) in adult patients (aged 18-64 years) who met DSM-IV-TR criteria for schizophrenia (Figure 18).[56]

Study 2 (Nakamura M, et al; 2009) was a 6-week, placebo-controlled trial (N = 180) designed to evaluate the efficacy and safety of a single once-daily dose of LATUDA (80 mg/day) in adult patients (aged 18-64 years) who met DSM-IV-TR criteria for schizophrenia (Figure 18).[57]

The primary endpoint of Studies 1 and 2 was the mean change from baseline in Brief Psychiatric Rating Scale derived (BPRSd) from the Positive and Negative Syndrome Scale (PANSS) total score at Week 6 by ANCOVA-LOCF analysis. A key secondary endpoint of Studies 1 and 2 was the mean change from baseline in Clinical Global Impressions-Severity of Illness Scale (CGI-S) score at Week 6 by ANCOVA-LOCF analysis.

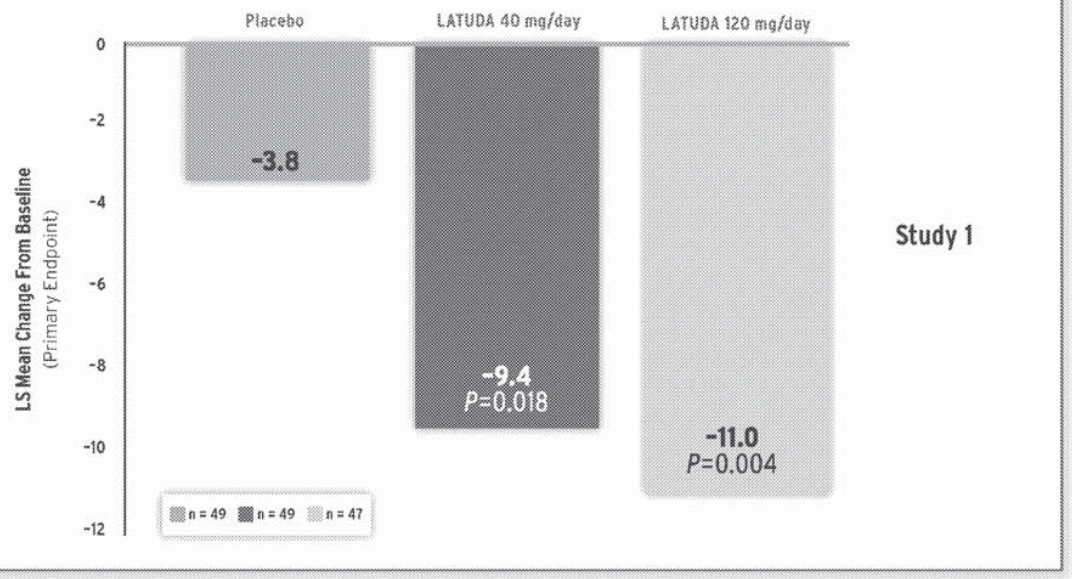
Figure 18. Designs of Studies 1 and 2 in Adult Patients[56,57]



Efficacy of LATUDA in Studies 1 and 2

In Study 1 (N = 145), both doses of LATUDA (40 and 120 mg/day) were superior to placebo for change in BPRSd score (primary endpoint) and CGI-S score (secondary endpoint) at 6 weeks (Figure 19, Table 4).[56]

Figure 19. LATUDA 40 mg/day and 120 mg/day (Study 1) Demonstrated Significant Efficacy in Adult Patients in BPRSd at Week 6[56]



Abbreviations: BPRSd, Brief Psychiatric Rating Scale derived; LS, least squares. Mean baseline BPRSd scores: LATUDA 40 mg/day 54.2, LATUDA 120 mg/day 52.7, placebo 54.7.

Table 4. LS Mean (SE) Change From Baseline to Week 6 in Adult Patients in CGI-S Compared With Placebo in Study 1 (N = 145)[56]

	Study 1		
Endpoint	**LATUDA 40 mg (n = 49)**	**LATUDA 120 mg (n = 47)**	**Placebo (n = 49)**
CGI-S	-0.8 (0.15)	-0.8 (0.14)	-0.1 (0.14)
P value vs placebo	0.002	0.001	—

Abbreviations: CGI-S, Clinical Global Impressions-Severity of Illness Scale; LS, least squares; SE, standard error.
Adult patients who met DSM-IV-TR criteria for schizophrenia (mean age 39.6 years, range 18-61 years).

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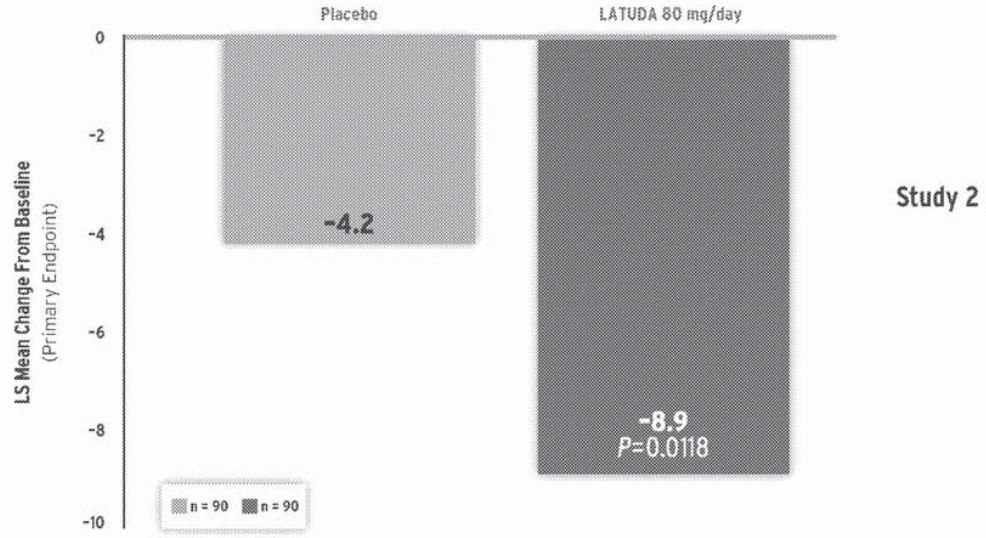
In Study 2 (N = 180), LATUDA 80 mg/day was superior to placebo for change in BPRSd (primary endpoint) and CGI-S scores (secondary endpoint) at 6 weeks (Figure 20, Table 5).[57]

Figure 20. LATUDA 80 mg/day (Study 2) Demonstrated Significant Efficacy in Adult Patients in BPRSd at Week 6[57]



Abbreviations: BPRSd, Brief Psychiatric Rating Scale derived; LS, least squares. Mean baseline BPRSd scores: LATUDA 80 mg/day 55.1, placebo 56.1.

Table 5. LS Mean (SE) Change From Baseline to Week 6 in Adult Patients in CGI-S Compared With Placebo in Study 2 (N = 180)[57]

	Study 2	
Endpoint	**LATUDA 80 mg (n = 90)**	**Placebo (n = 90)**
CGI-S	-0.6 (0.1)	-0.2 (0.1)
P value vs placebo	0.0072	—

Abbreviations: CGI-S, Clinical Global Impressions-Severity of Illness Scale; LS, least squares; SE, standard error.
Adult patients who met DSM-IV-TR criteria for schizophrenia (mean age 40.8 years, range 21-63 years).

Study 3

Study 3 (Meltzer HY, et al; 2011) was a 6-week, placebo- and active-controlled trial (N = 473) designed to evaluate the efficacy and safety of 2 fixed, once-daily doses of LATUDA (40 mg/day or 120 mg/day). Olanzapine 15 mg/day was included as an active control to establish assay sensitivity; however, this study was not designed for a head-to-head comparison of LATUDA and olanzapine (Figure 21).[58] An open-label extension of Study 3 (Stahl SM, et al; 2013) evaluated the safety and tolerability of LATUDA 40 mg/day to 120 mg/day in patients continued on or transitioned to LATUDA from the original 6-week study.[59]

Study 4

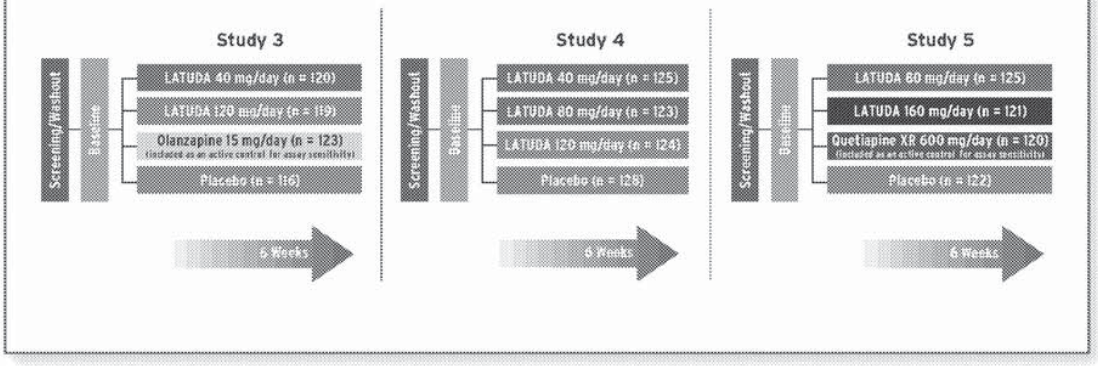
Study 4 (Nasrallah HA, et al; 2013) was a 6-week, placebo-controlled trial (N = 489) designed to evaluate the efficacy and safety of 3 fixed once-daily doses of LATUDA (40 mg/day, 80 mg/day, 120 mg/day) (Figure 21).[60]

Study 5

Study 5 (Loebel A, et al; 2013) was a 6-week, randomized, double-blind, placebo- and active-controlled trial (N = 488) designed to evaluate the safety and efficacy of 2 fixed, once-daily doses of LATUDA (80 mg/day or 160 mg/day). Quetiapine XR 600 mg/day was included as an active control to establish assay sensitivity; however, the study was not designed for comparison of LATUDA and quetiapine XR (Figure 21).[61]

Each study enrolled adult patients (age range 18–75 years) who met DSM-IV-TR criteria for schizophrenia. The primary endpoint of each study was the mean change from baseline in PANSS total score at Week 6 by MMRM analysis. Secondary endpoint was the mean change from baseline in CGI-S score at Week 6 by MMRM analysis.

Figure 21. Designs of Studies 3, 4, and 5 in Adult Patients[58,60,61]



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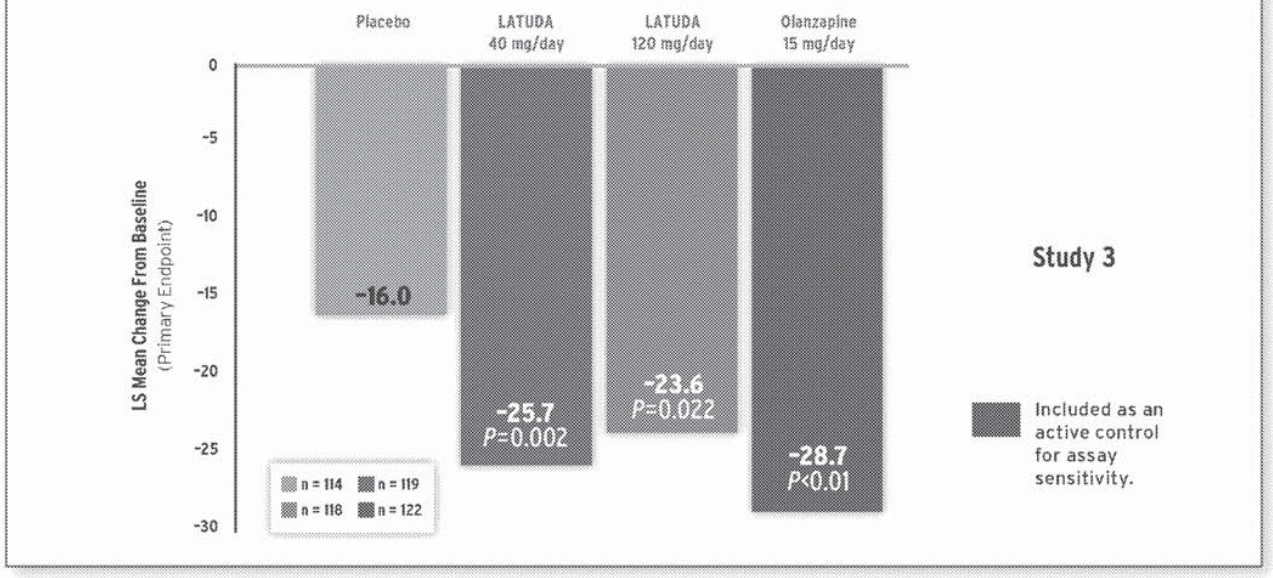
Efficacy of LATUDA in Studies 3, 4, and 5

In Study 3 (N = 473), both doses of LATUDA (40 and 120 mg/day), as well as olanzapine (15 mg/day), were superior to placebo in reducing PANSS (primary endpoint) and CGI-S scores (secondary endpoint) at 6 weeks (Figure 22, Table 6). Olanzapine was used as an active control to test assay sensitivity, and the study was not designed for a comparison of LATUDA and olanzapine.[58]

Figure 22. LATUDA 40 mg/day and 120 mg/day (Study 3) Demonstrated Significant Efficacy in Adult Patients in PANSS Total Score at Week 6[58]



P values for the comparisons vs placebo were adjusted for multiple comparisons, except for olanzapine.
Abbreviations: LS, least squares; PANSS, Positive and Negative Syndrome Scale. Mean baseline PANSS total scores: LATUDA 40 mg/day 96.6, LATUDA 120 mg/day 97.9, olanzapine 15 mg/day 96.3, placebo 95.8.

Table 6. LS Mean (SE) Change From Baseline to Week 6 in Adult Patients in CGI-S Compared With Placebo in Study 3 (N = 473)[58]

	Study 3			
Endpoint	**LATUDA 40 mg (n = 119)**	**LATUDA 120 mg (n = 118)**	**Olanzapine 15 mg Active Control (n = 122)**	**Placebo (n = 114)**
CGI-S	-1.5 (0.1)	-1.4 (0.1)	-1.5 (0.1)	-1.1 (0.1)
P value vs placebo	0.011	0.040	<0.001	--

P values for the comparisons vs placebo were adjusted for multiple comparisons, except for olanzapine.
Abbreviations: CGI-S, Clinical Global Impressions-Severity of Illness Scale; LS, least squares; SE, standard error.
Adult patients who met DSM-IV-TR criteria for schizophrenia (mean age 37.7 years, range 18-68 years).

Summary of Results From the 26-Week Open-label Extension Phase of Study 3[59]

Patients who elected to enter the 6-month open-label extension phase entered a single-blind 3-day placebo washout phase before transitioning to LATUDA 80 mg/day in an open-label fashion. Of 254 enrolled patients, 113 (44.5%) completed 6 months of open-label treatment.

Safety and tolerability results from the 26-week open-label extension were consistent with the 6-week study and uncontrolled longer-term, primarily open-label extension studies of LATUDA.

Small decreases were observed in mean weight (-0.1 kg) and median lipid levels (total cholesterol, -6.5 mg/dL; low-density lipoprotein, 0.0 mg/dL; high-density lipoprotein, 0.0 mg/dL; triglycerides, -8.5 mg/dL) with LATUDA. No clinically meaningful changes were observed in median prolactin levels. The 2 most commonly reported adverse events were akathisia (13.0%) and insomnia (11.0%).

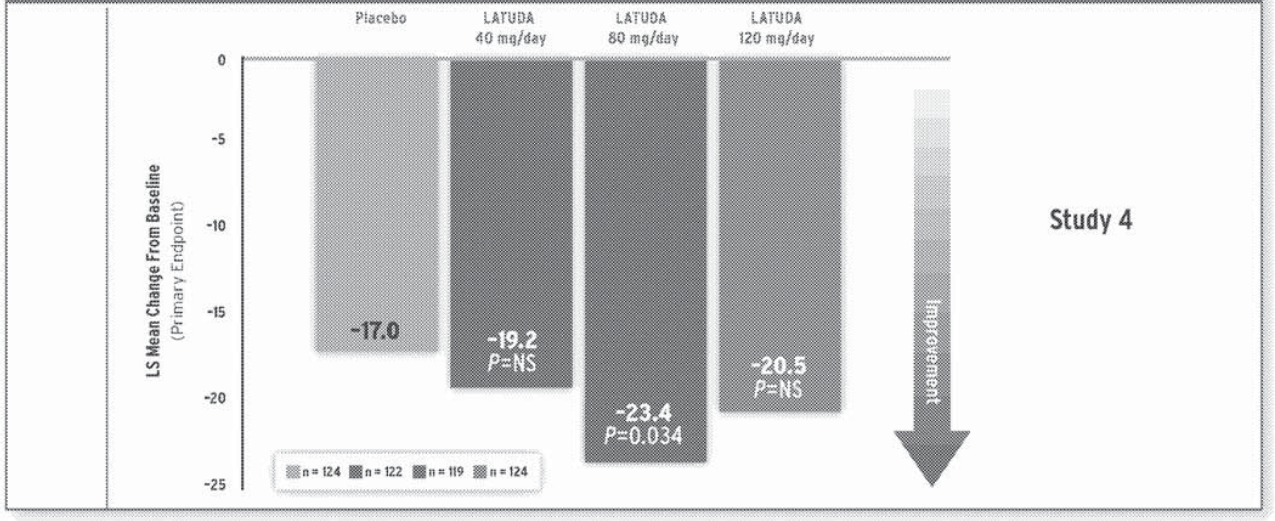
Persistent antipsychotic efficacy of LATUDA was shown for patients who had previously received LATUDA, olanzapine, or placebo, and further reductions from open-label baseline to final visit were observed in mean PANSS total score (-8.7) for all patients.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

In Study 4 (N = 489), LATUDA 80 mg/day was superior to placebo in reducing PANSS (primary endpoint) and CGI-S scores (secondary endpoint) at 6 weeks (Figure 23, Table 7).[60] The 40-mg and 120-mg doses also reduced PANSS scores, but these results did not reach statistical significance compared with placebo.

Figure 23. LATUDA 80 mg/day (Study 4) Demonstrated Significant Efficacy in Adult Patients in PANSS Total Score at Week 6[60]



P values for the comparisons vs placebo were adjusted for multiple comparisons.
Abbreviations: LS, least squares; PANSS, Positive and Negative Syndrome Scale.
Mean baseline PANSS total scores: LATUDA 40 mg/day 96.5, LATUDA 80 mg/day 96.0, LATUDA 120 mg/day 96.0, placebo 96.8.

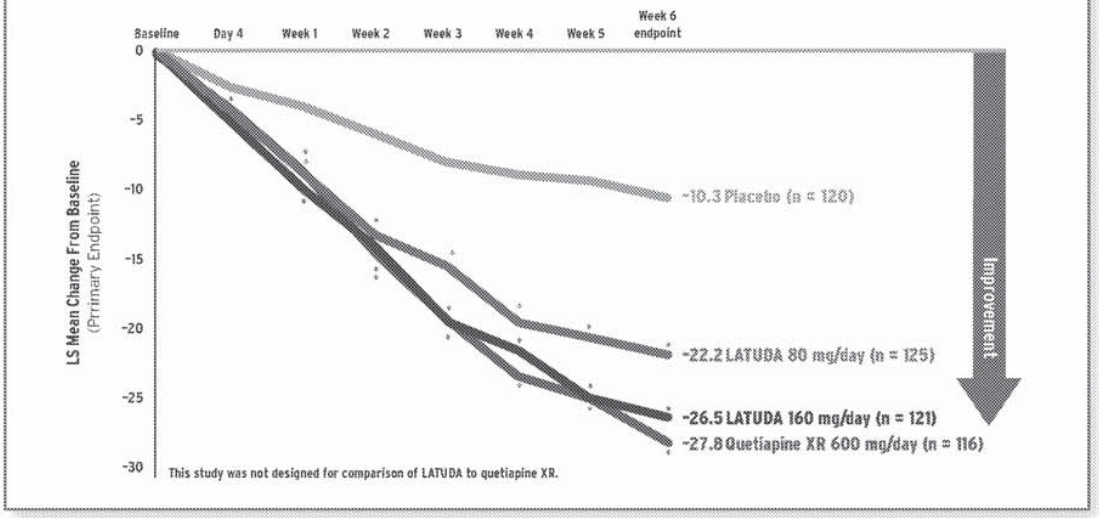
Table 7. LS Mean (SE) Change From Baseline to Week 6 in Adult Patients in CGI-S Compared With Placebo in Study 4 (N = 489)[60]

	Study 4			
Endpoint	**LATUDA 40 mg (n = 122)**	**LATUDA 80 mg (n = 119)**	**LATUDA 120 mg (n = 124)**	**Placebo (n = 124)**
CGI-S	-1.1 (0.1)	-1.4 (0.1)	-1.2 (0.1)	-1.0 (0.1)
P value vs placebo	NS	0.034	NS	--

P values for the comparisons vs placebo were adjusted for multiple comparisons.
Abbreviations: CGI-S, Clinical Global Impressions-Severity of Illness Scale; LS, least squares; NS, not significant; SE, standard error.
Adult patients who met DSM-IV-TR criteria for schizophrenia (mean age 38.8 years, range 18-72 years).

In Study 5 (N = 488), LATUDA 80 mg/day and 160 mg/day were superior to placebo in reducing PANSS (primary endpoint) and CGI-S (secondary endpoint) scores at 6 weeks (Figure 24, Table 8).[61] The active control quetiapine XR 600 mg/day also significantly reduced both PANSS and CGI-S scores compared with placebo.

Figure 24. LATUDA 80 mg/day and 160 mg/day (Study 5) Demonstrated Significant Efficacy in Adult Patients in PANSS Total Score at Week 6[61]



†$P<0.001$ vs placebo.
Abbreviations: LS, least squares; PANSS, Positive and Negative Syndrome Scale.
Mean baseline PANSS total scores: LATUDA 80 mg/day 97.7, LATUDA 160 mg/day 97.5, quetiapine extended release 600 mg/day 97.7, placebo 96.6.

Table 8. LS Mean (SE) Change From Baseline to Week 6 in Adult Patients in CGI-S Compared With Placebo in Study 5 (N = 488)[61]

	Study 5			
Endpoint	**LATUDA 80 mg (n = 125)**	**LATUDA 160 mg (n = 121)**	**Quetiapine XR 600 mg (n = 116)**	**Placebo (n = 120)**
CGI-S	-1.5 (0.1)	-1.7 (0.1)	-1.7 (0.1)	-0.9 (0.1)
P value vs placebo	<0.001	<0.001	<0.001	--

P values for the comparisons vs placebo were adjusted for multiple comparisons.
Abbreviations: CGI-S, Clinical Global Impressions-Severity of Illness Scale; LS, least squares; SE, standard error.
Adult patients who met DSM-IV-TR criteria for schizophrenia (mean age 37.2 years, range 18-65 years).

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

LATUDA Efficacy Summary of Adult Studies in Schizophrenia

Table 9. Primary Efficacy Results for Studies in Adult Patients With Schizophrenia (BPRSd or PANSS Scores)[51]

Study	Treatment Group	Primary Efficacy Measure: BPRSd		
		Mean Baseline Score (SD)	LS Mean Change From Baseline (SE)	Placebo-Subtracted Difference[a] (95% CI)
1	LATUDA (40 mg/day)*	54.2 (8.8)	-9.4 (1.6)	-5.6 (-9.8, -1.4)
	LATUDA (120 mg/day)*	52.7 (7.6)	-11.0 (1.6)	-6.7 (-11.0, -2.5)
	Placebo	54.7 (8.1)	-3.8 (1.6)	--
2	LATUDA (80 mg/day)*	55.1 (6.0)	-8.9 (1.3)	-4.7 (-8.3, -1.1)
	Placebo	56.1 (6.8)	-4.2 (1.4)	--
		Primary Efficacy Measure: PANSS		
3	LATUDA (40 mg/day)*	96.6 (10.7)	-25.7 (2.0)	-9.7 (-15.3, -4.1)
	LATUDA (120 mg/day)*	97.9 (11.3)	-23.6 (2.1)	-7.5 (-13.4, -1.7)
	Olanzapine (15 mg/day)*[b] (active control)	96.3 (12.2)	-28.7 (1.9)	-12.6 (-18.2, -7.9)
	Placebo	95.8 (10.8)	-16.0 (2.1)	--
4	LATUDA (40 mg/day)	96.5 (11.5)	-19.2 (1.7)	-2.1 (-7.0, 2.8)
	LATUDA (80 mg/day)*	96.0 (10.8)	-23.4 (1.8)	-6.4 (-11.3, -1.5)
	LATUDA (120 mg/day)	96.0 (9.7)	-20.5 (1.8)	-3.5 (-8.4, 1.4)
	Placebo	96.8 (11.1)	-17.0 (1.8)	--
5	LATUDA (80 mg/day)*	97.7 (9.7)	-22.2 (1.8)	-11.9 (-16.9, -6.9)
	LATUDA (160 mg/day)*	97.5 (11.8)	-26.5 (1.8)	-16.2 (-21.2, -11.2)
	Quetiapine extended-release (600 mg/day)*[b] (active control)	97.7 (10.2)	-27.8 (1.8)	-17.5 (-22.5, -12.4)
	Placebo	96.6 (10.2)	-10.3 (1.8)	--

Abbreviations: SD, standard deviation; SE, standard error; LS, least squares; CI, confidence interval, unadjusted for multiple comparisons; PANSS, Positive and Negative Syndrome Scale; BPRSd, Brief Psychiatric Rating Scale derived.

[a]Difference (drug minus placebo) in least-squares mean change from baseline.

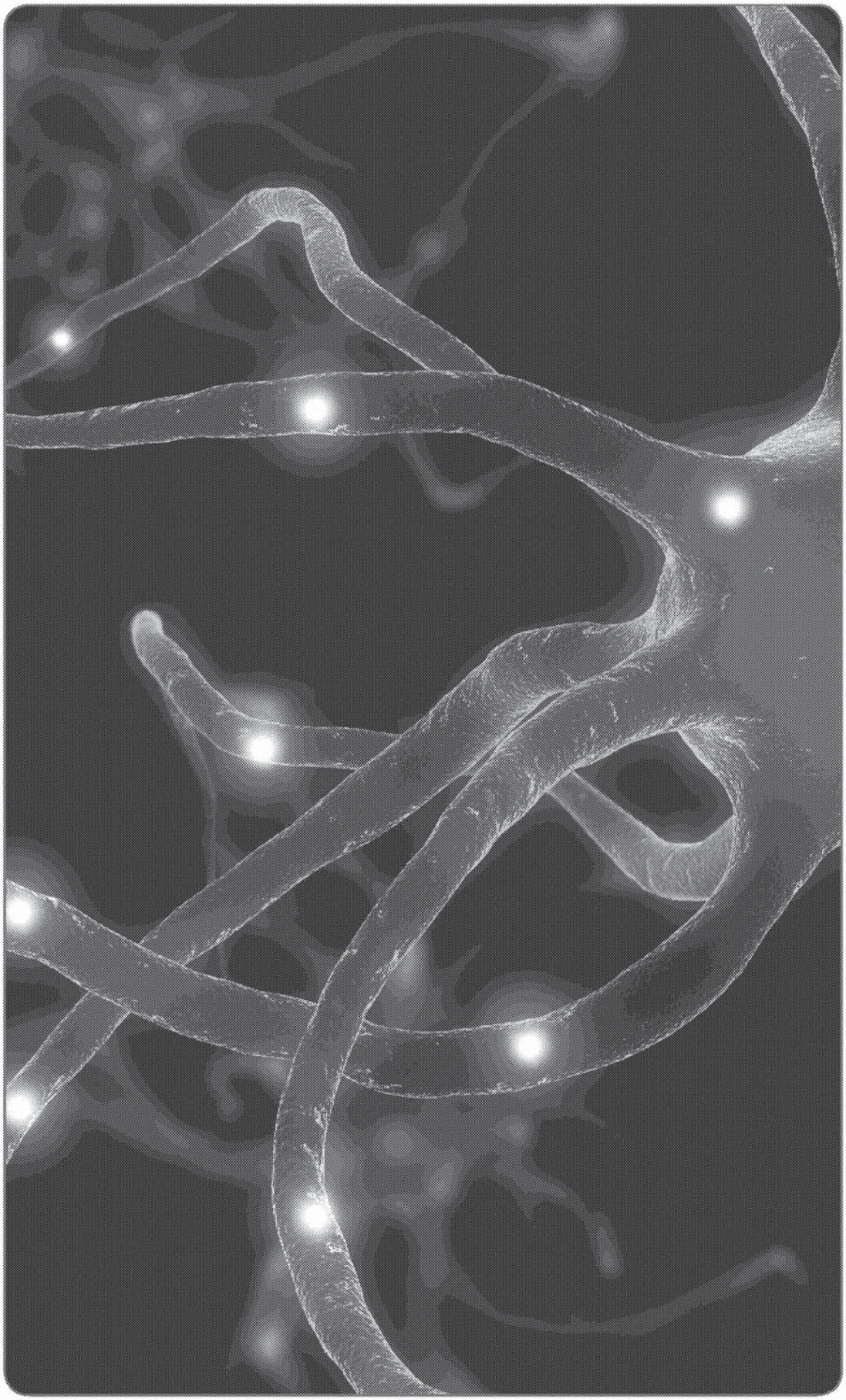
[b]Included for assay sensitivity.

*Doses statistically significantly superior to placebo.

IMPORTANT SAFETY INFORMATION FOR LATUDA

Dysphagia: Antipsychotics, including LATUDA, have been associated with esophageal dysmotility and aspiration, and should be used with caution in patients at risk for aspiration pneumonia.

Latuda® (lurasidone HCl) tablets
20mg | 40mg | 60mg | 80mg | 120mg

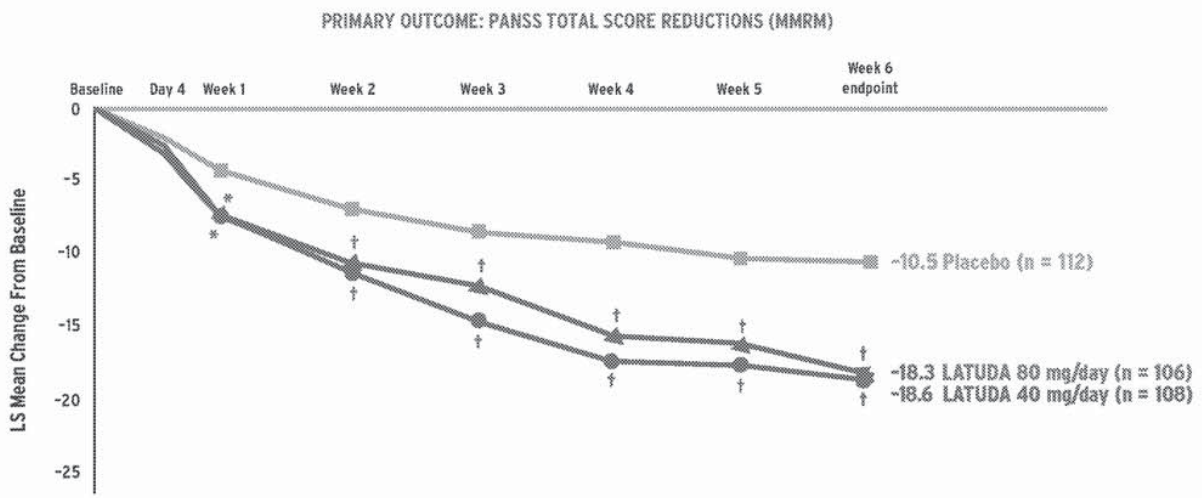


Adolescents

Symptom improvement in adolescents with schizophrenia was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adolescent patients (13-17 years) with schizophrenia. Patients met DSM-IV-TR criteria for schizophrenia (N = 326). Patients were randomized to one of two fixed doses of LATUDA (40 or 80 mg/day) or placebo.[62]

In this study, LATUDA showed statistically significant and clinically meaningful symptom improvement on the primary rating instrument of the PANSS total score compared to placebo (Figure 25).[51,62]

Figure 25. LATUDA 40 mg/day and 80 mg/day Significantly Improved PANSS Total Scores vs Placebo in Adolescents[51,62]



*$P \leq 0.05$ vs placebo; †$P \leq 0.01$ vs placebo.
Abbreviations: PANSS, Positive and Negative Syndrome Scale; MMRM, Mixed model for repeated measures.
Mean PANSS scores: LATUDA 40 mg/day, 94.5; LATUDA 80 mg/day, 94.0; placebo, 92.8.

Significant reductions were also seen in the key secondary endpoint of CGI-S score from baseline vs placebo at Week 6 (Table 10).[62] On average, for both PANSS and CGI-S, the 80-mg/day dose did not provide additional benefit compared to the 40-mg/day dose.

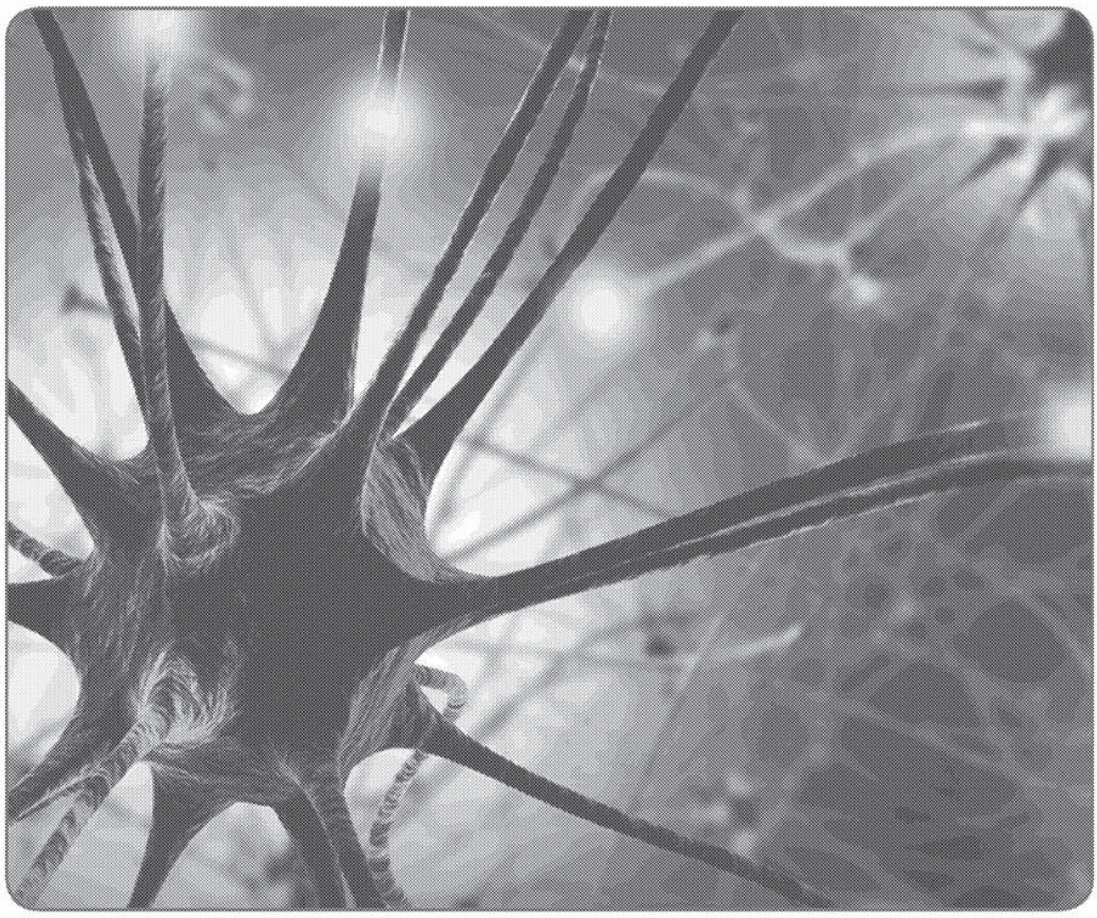
Table 10. LATUDA 40 mg/day and 80 mg/day Significantly Improved CGI-S Scores vs Placebo in Adolescents[62]

Key Secondary Outcome: CGI-S score reduction at Week 6 (MMRM)		
Placebo (n = 93)	**LATUDA 40 mg/day (n = 96)**	**LATUDA 80 mg/day (n = 97)**
-0.5	-1.0*	-0.9†

*$P = 0.0003$ vs placebo; †$P = 0.0015$ vs placebo.
Mean CGI-S scores at baseline: LATUDA 40 mg/day, 4.9; LATUDA 80 mg/day, 4.8; placebo, 4.8.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Latuda® (lurasidone HCl) tablets
20mg | 40mg | 60mg | 80mg | 120mg



LATUDA Safety & Tolerability

LATUDA Safety Database: Adults With Bipolar Depression and Schizophrenia

- 3799 adult patients exposed to 1 or more doses of LATUDA for the treatment of schizophrenia and bipolar depression in placebo-controlled studies
  - 1106 LATUDA-treated patients had at least 24 weeks of exposure
  - 371 LATUDA-treated patients had at least 52 weeks of exposure
- 1251 patient-years total experience

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Major Depressive Episodes Associated With Bipolar I Disorder (Bipolar Depression)

Adverse Reactions (ARs) With LATUDA

Monotherapy bipolar depression study

In the monotherapy study, the most common ARs (incidence ≥5% in either dose group and at least twice the rate of placebo) in patients treated with LATUDA were akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety.

Table 11 shows ARs that occurred in 2% or more of LATUDA-treated patients on monotherapy and that occurred at greater incidence than in placebo-treated patients. Safety data showed that treatment with LATUDA (20-120 mg/day, flexibly dosed) as monotherapy was safe and well tolerated in patients with bipolar depression.

Table 11. Adverse Reactions in ≥2% of LATUDA-Treated Patients and Greater Incidence Than Placebo-Treated Patients in the Monotherapy Bipolar Depression Study[51]

Adverse Reaction	LATUDA 20-60 mg (n = 164)	LATUDA 80-120 mg (n = 167)	Placebo (n = 168)
Nausea	10%	17%	8%
Somnolence*	7%	14%	7%
Akathisia	8%	11%	2%
Extrapyramidal symptoms†	5%	9%	2%
Dry mouth	6%	4%	4%
Vomiting	2%	6%	2%
Diarrhea	5%	3%	2%
Anxiety	4%	5%	1%
Nasopharyngitis	4%	4%	1%
Back pain	3%	<1%	<1%
Urinary tract infections	2%	1%	<1%
Influenza	<1%	2%	1%

*Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence.

†Extrapyramidal symptoms include adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus.

IMPORTANT SAFETY INFORMATION FOR LATUDA

Most Commonly Observed Adverse Reactions: Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo) for LATUDA:

- Adult patients with bipolar depression: akathisia, extrapyramidal symptoms, and somnolence
- Adult patients with schizophrenia: somnolence, akathisia, extrapyramidal symptoms, and nausea
- Adolescent patients (13 to 17 years) with schizophrenia: somnolence, nausea, akathisia, extrapyramidal symptoms (non-akathisia), vomiting, and rhinorrhea/rhinitis

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 877-737-7226 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Dose-related ARs in the Monotherapy Bipolar Depression Study

In the short-term, placebo-controlled study (involving lower and higher LATUDA dose ranges), ARs that occurred with a >5% incidence in the patients treated with LATUDA in any dose group and greater than placebo in both groups were nausea (10.4%, 17.4%), somnolence (7.3%, 13.8%), akathisia (7.9%, 10.8%), and extrapyramidal symptoms (4.9%, 9.0%) for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively.

Adjunctive Therapy Bipolar Depression Studies (Safety Analysis Includes a Second Adjunctive Therapy Study)

In the adjunctive therapy studies, the most common ARs (incidence ≥5% and at least twice the rate of placebo) in patients treated with LATUDA were akathisia and somnolence. Table 12 shows ARs that occurred in 2% or more of LATUDA-treated patients on adjunctive therapy and that occurred at greater incidence than in placebo-treated patients. The pooled safety data showed that treatment with LATUDA (20-120 mg/day, flexibly dosed) adjunctive to lithium or valproate was safe and well tolerated in patients with bipolar depression.

Table 12. Adverse Reactions in ≥2% of LATUDA-Treated Patients and More Frequently Than in Placebo-Treated Patients in the Adjunctive Therapy Bipolar Depression Studies (Pooled Analysis of 2 Studies)[51]

Adverse Reaction	LATUDA 20-120 mg + Li/VPA (N = 360)	Placebo + Li/VPA (N = 334)
Nausea	14%	10%
Extrapyramidal symptoms*	14%	9%
Somnolence†	11%	5%
Akathisia	11%	5%
Vomiting	4%	1%
Nasopharyngitis	4%	2%
Restlessness	4%	<1%
Fatigue	3%	1%
Increased appetite	3%	1%
Weight increased	3%	<1%

*Extrapyramidal symptoms include adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus.

†Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence.

Abbreviations: Li, lithium; VPA, valproate.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

ARs Leading to Discontinuation

Monotherapy bipolar depression study

A total of 6.0% of LATUDA-treated patients and 5.4% of placebo-treated patients discontinued due to ARs. There were no ARs associated with discontinuation in patients treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adjunctive therapy bipolar depression studies

A total of 5.8% of LATUDA-treated patients and 4.8% of placebo-treated patients discontinued due to ARs. There were no ARs associated with discontinuation in patients treated with LATUDA that were at least 2% and at least twice the placebo rate.

Extrapyramidal Symptoms (EPS)

Monotherapy bipolar depression study

In the short-term, placebo-controlled monotherapy bipolar depression study for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness, was 6.9% versus 2.4% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 9.4% versus 2.4% for placebo-treated patients.

Adjunctive therapy bipolar depression studies

In the short-term, placebo-controlled adjunctive therapy bipolar depression studies for LATUDA-treated patients, the incidence of EPS, excluding akathisia and restlessness, was 13.9% versus 8.7% for placebo. The incidence of akathisia for LATUDA-treated patients was 10.8% versus 4.8% for placebo-treated patients.

Vital signs

There were no dose-related or clinically meaningful effects of LATUDA on vital sign parameters (blood pressure, pulse, body temperature) either in the monotherapy or adjunctive therapy studies.

IMPORTANT SAFETY INFORMATION FOR LATUDA

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

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. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Suicidal Thoughts and Behaviors
Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behavior. LATUDA is not approved for use in pediatric patients with depression.

Metabolic Changes[51]

Changes in Glucose

Monotherapy bipolar depression study

Changes in glucose from the short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are shown in Table 13.

Table 13. Mean Change in Fasting Glucose From Baseline in the Monotherapy Bipolar Depression Study[51]

Placebo	LATUDA 20-60 mg/day	LATUDA 80-120 mg/day
Mean Change From Baseline (mg/dL)		
n = 148	n = 140	n = 143
+1.8	-0.8	+1.8

Adjunctive therapy bipolar depression studies

Changes in glucose from pooled short-term, flexible-dosed, placebo-controlled, adjunctive therapy bipolar depression studies are shown in Table 14.

Table 14. Mean Change in Fasting Glucose From Baseline in the Adjunctive Therapy Bipolar Depression Studies[51]

Placebo	LATUDA 20-120 mg/day
Mean Change From Baseline (mg/dL)	
n = 302	n = 319
-0.9	+1.2

Glucose changes in longer-term uncontrolled bipolar depression studies

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term study, and continued in the longer-term study, had a mean change in glucose of 1.2 mg/dL at Week 24 (n = 129). Patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study had a mean change in glucose of 1.7 mg/dL at Week 24 (n = 88).

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Changes in Lipids

Monotherapy bipolar depression study

Changes in lipids from the short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are shown in Table 15.

Table 15. Mean Change in Fasting Lipids From Baseline in the Monotherapy Bipolar Depression Study[51]

	Placebo	LATUDA 20-60 mg/day	LATUDA 80-120 mg/day
Mean Change From Baseline (mg/dL)			
	n = 147	n = 140	n = 144
Total Cholesterol	-3.2	+1.2	-4.6
Triglycerides	+6.0	+5.6	+0.4

Adjunctive therapy bipolar depression studies

Changes in lipids from pooled short-term, flexible-dosed, placebo-controlled, adjunctive therapy bipolar depression studies are shown in Table 16.

Table 16. Mean Change in Fasting Lipids From Baseline in the Adjunctive Therapy Bipolar Depression Studies[51]

	Placebo	LATUDA 20-120 mg/day
Mean Change From Baseline (mg/dL)		
	n = 303	n = 321
Total Cholesterol	-2.9	-3.1
Triglycerides	-4.6	+4.6

Lipid changes in longer-term uncontrolled bipolar depression studies

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.5 (n = 130) and -1.0 (n = 130) mg/dL at Week 24, respectively. In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.9 (n = 88) and 5.3 (n = 88) mg/dL at Week 24, respectively.

Changes in Weight

Monotherapy bipolar depression study

Changes in weight from the short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are shown in Table 17. The mean weight gain was 0.29 kg for LATUDA-treated patients compared with -0.04 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight at the end of the study was 2.4% for LATUDA-treated patients versus 0.7% for placebo-treated patients.

Table 17. Mean Change in Weight (kg) From Baseline in the Monotherapy Bipolar Depression Study[51]

Placebo (n = 151)	LATUDA 20-60 mg/day (n = 143)	LATUDA 80-120 mg/day (n = 147)
-0.04	+0.56	+0.02

Adjunctive therapy bipolar depression studies

Changes in weight from the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 18. The mean weight gain was 0.11 kg for LATUDA-treated patients compared to 0.16 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight at the end of the study was 3.1% for LATUDA-treated patients versus 0.3% for placebo-treated patients.

Table 18. Mean Change in Weight (kg) From Baseline in the Adjunctive Therapy Bipolar Depression Studies[51]

Placebo (n = 307)	LATUDA 20-120 mg/day (n = 327)
+0.16	+0.11

Weight changes in longer-term uncontrolled bipolar depression studies

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in weight of -0.02 kg at Week 24 (n = 130). In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA as adjunctive therapy with either lithium or valproate in the short-term study, and continued in the longer-term study, had a mean change in weight of 1.28 kg at Week 24 (n = 86).

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

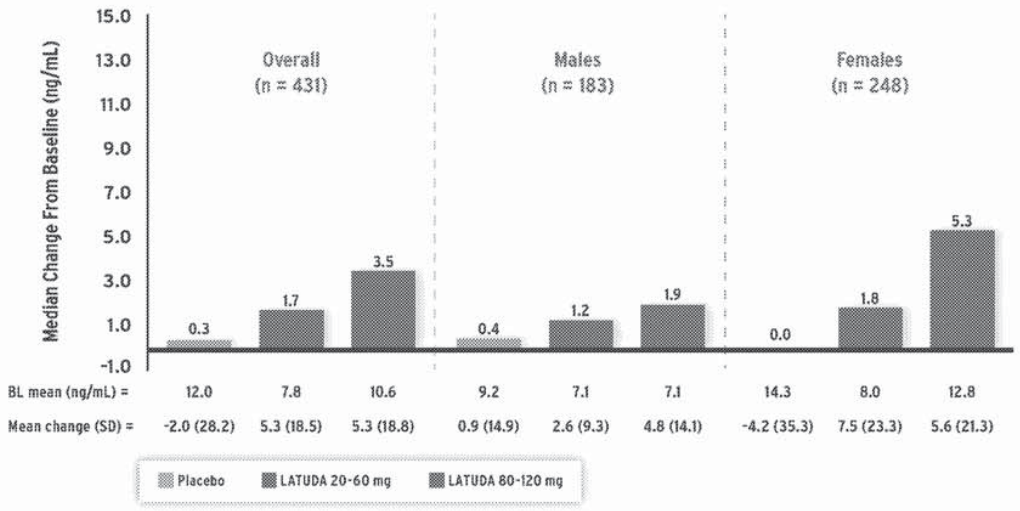
Changes in Prolactin

Monotherapy bipolar depression study

The median change from baseline to endpoint in prolactin levels in the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study was +1.7 ng/mL with LATUDA 20 to 60 mg/day and +3.5 ng/mL with 80 to 120 mg/day compared to +0.3 ng/mL with placebo-treated patients (Figure 26). The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL.

The proportion of patients with prolactin elevations ≥5x the upper limit of normal (ULN) was 0.4% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5x ULN was 0.6% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% versus 0% for placebo-treated male patients.

Figure 26. Median Change in Prolactin From Baseline in the Monotherapy Bipolar Depression Study[51]



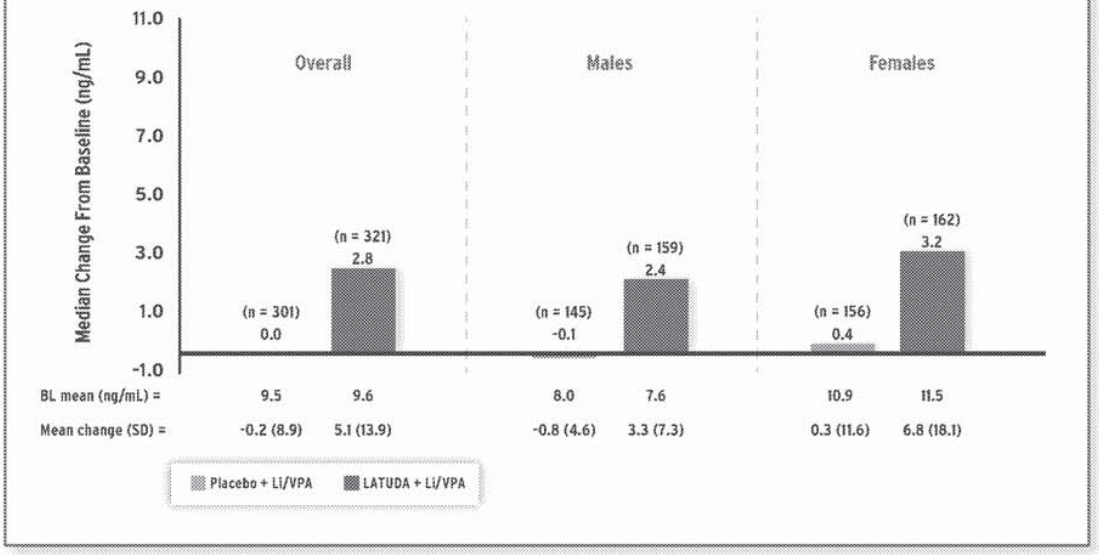
Abbreviations: BL, baseline; SD, standard deviation.

Adjunctive therapy bipolar depression studies

The median change from baseline to endpoint in prolactin levels in the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies was +2.8 ng/mL with LATUDA 20 to 120 mg/day compared to 0.0 ng/mL with placebo-treated patients (Figure 27). The median change from baseline to endpoint for males was +2.4 ng/mL and for females was +3.2 ng/mL.

The proportion of patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% versus 0% for placebo-treated male patients.

Figure 27. Median Change in Prolactin From Baseline in the Adjunctive Therapy Bipolar Depression Studies[51]



Abbreviations: BL, baseline; Li, lithium; SD, standard deviation; VPA, valproate.

Prolactin Changes in Longer-term Uncontrolled Bipolar Depression Studies

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA as monotherapy in the short-term and continued in the longer-term study had a median change in prolactin of -1.15 ng/mL at Week 24 (n = 130). In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study had a median change in prolactin of -2.9 ng/mL at Week 24 (n = 88).

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

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Schizophrenia

Adverse Reactions With LATUDA

Adults

The most commonly observed ARs (≥5% and at least twice the rate of placebo) in patients treated with LATUDA in short-term clinical studies were somnolence, akathisia, extrapyramidal symptoms, and nausea.

ARs occurring in ≥2% of LATUDA-treated patients during the short-term 6-week trials of patients with schizophrenia are shown in Table 19.

Table 19. Adverse Reactions in ≥2% of LATUDA-Treated Patients and Occurring at Greater Incidence Than in the Placebo-Treated Patients in Adult 6-Week Schizophrenia Trials*[1,5]

Body System or Organ Class	Placebo (n = 708) (%)	LATUDA 20 mg/day (n = 71) (%)	LATUDA 40 mg/day (n = 487) (%)	LATUDA 80 mg/day (n = 538) (%)	LATUDA 120 mg/day (n = 291) (%)	LATUDA 160 mg/day (n = 121) (%)	All LATUDA (n = 1508) (%)
Gastrointesinal Disorders							
Nausea	5	11	10	9	13	7	10
Vomiting	6	7	6	9	9	7	8
Dyspepsia	5	11	6	5	8	6	6
Salivary Hypersecretion	<1	1	1	2	4	2	2
Musculoskeletal and Connective Tissue Disorders							
Back Pain	2	0	4	3	4	0	3
Nervous System Disorders							
Somnolence*	7	15	16	15	26	8	17
Akathisia	3	6	11	12	22	7	13
Extrapyramidal Disorder†	6	6	11	12	22	13	14
Dizziness	2	6	4	4	5	6	4
Psychiatric Disorders							
Insomnia	8	8	10	11	9	7	10
Agitation	4	10	7	3	6	5	5
Anxiety	4	3	6	4	7	3	5
Restlessness	1	1	3	1	3	2	2

Note: Figures rounded to the nearest integer.

*Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence.

†Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Dose-related ARs in Pooled 6-week Trials

Akathisia and extrapyramidal symptoms were dose related. The frequency of akathisia increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 10.7% for LATUDA 40 mg, 12.3% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg). Akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo. The frequency of extrapyramidal symptoms increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 11.5% for LATUDA 40 mg, 11.9% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg) (Table 20).

Table 20. Dose-Related Increase in Akathisia in Adult Pooled, 6-Week, Placebo-Controlled Studies[51]

	LATUDA 20 mg (n = 71)	LATUDA 40 mg (n = 487)	LATUDA 80 mg (n = 538)	LATUDA 120 mg (n = 291)	LATUDA 160 mg (n = 121)	Placebo (n = 709)
Akathisia (%)	5.6	10.7	12.3	22.0	7.4	3.0

ARs Leading to Discontinuation

A total of 9.5% (143/1508) LATUDA-treated patients and 9.3% (66/708) of placebo-treated patients discontinued due to ARs. There were no ARs associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adolescents

The following findings are based on the short-term, placebo-controlled adolescent study for schizophrenia in which LATUDA was administered at daily doses ranging from 40 (n = 110) to 80 mg (n = 104). The most common ARs (incidence ≥5% and at least twice the rate of placebo) in adolescent patients (13-17 years) treated with LATUDA were somnolence, nausea, akathisia, extrapyramidal symptoms (non-akathisia, 40 mg only), vomiting, and rhinorrhea/rhinitis (80 mg only).

Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in adolescent patients with schizophrenia) are shown in Table 21.

Table 21. Adverse Reactions in ≥2% of LATUDA-Treated Adolescent Patients and Occurring at Greater Incidence Than in Placebo-Treated Adolescent Patients in the 6-Week Schizophrenia Study[5]

Body System or Organ Class	Placebo (n = 112) (%)	LATUDA 40 mg/day (n = 110) (%)	LATUDA 80 mg/day (n = 104) (%)	All LATUDA (n = 214) (%)
Gastrointesinal Disorders				
Nausea	3	13	14	14
Vomiting	2	8	6	8
Diarrhea	1	3	5	4
Dry Mouth	0	2	3	2
Infections and Infestations				
Viral infection*	6	11	10	10
Rhinitis†	2	<1	8	4
Oropharyngeal Pain	0	<1	3	2
Tachycardia	0	0	3	1
Nervous System Disorders				
Somnolence‡	7	15	13	15
Akathisia	2	9	9	9
Dizziness	1	5	5	5

*Viral infection includes adverse event terms: nasopharyngitis, influenza, viral infection, and upper respiratory tract infection.
†Rhinitis includes adverse event terms: rhinitis, allergic rhinitis, rhinorrhea, and nasal congestion.
‡Somnolence includes adverse event terms: hypersomnia, sedation, and somnolence.

The incidence of extrapyramidal symptoms (non-akathisia)[§] for LATUDA-treated patients was higher in the 40-mg (10%) and 80-mg (7.7%) treatment groups vs placebo (3.6%).

§Extrapyramidal symptoms (non-akathisia) includes adverse event terms: bradykinesia, drooling, dyskinesia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, parkinsonism, psychomotor retardation, dystonia, trismus, oculogyric crisis, oromandibular dystonia, tongue spasm, and torticollis.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

ARs Leading to Discontinuation

The incidence of discontinuation due to ARs in LATUDA- and placebo-treated patients (13-17 years) was 4% and 8%, respectively.

Extrapyramidal Symptoms (EPS)

Adults

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness, was 13.5% versus 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% versus 3.0% for placebo-treated patients.

Adolescents

In the short-term, placebo-controlled study of schizophrenia in adolescents, the incidence of EPS,* excluding events related to akathisia, for LATUDA-treated patients was higher in the 40-mg (10%) and the 80-mg (7.7%) treatment groups vs placebo (3.6%); and the incidence of akathisia-related events for LATUDA-treated patients was 8.9% vs 1.8% for placebo-treated patients.

*EPS (non-akathisia) includes adverse event terms: bradykinesia, drooling, dyskinesia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, parkinsonism, psychomotor retardation, dystonia, trismus, oculogyric crisis, oromandibular dystonia, tongue spasm, and torticollis.

Metabolic Changes

Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness.

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

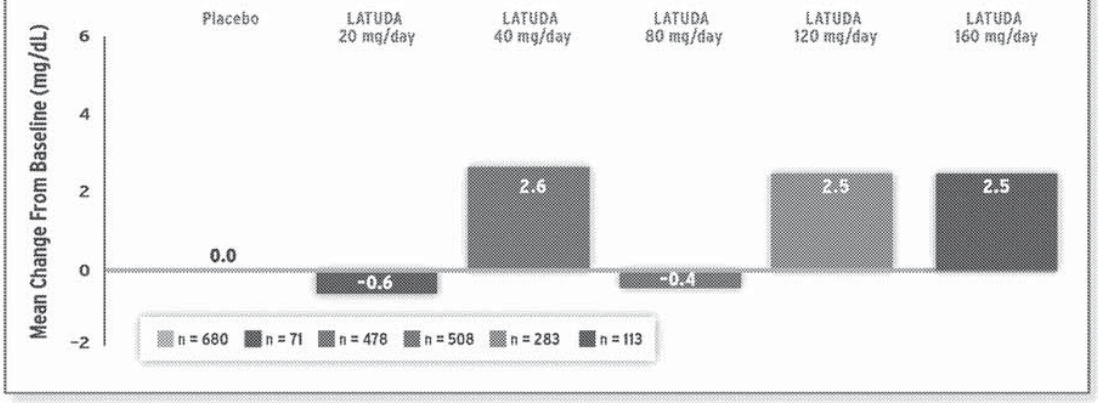
Weight gain has been observed with use of atypical antipsychotics. Clinical monitoring of weight is recommended.

Changes in Glucose

Adults

Changes in glucose from pooled data from short-term, placebo-controlled studies in adults are shown in Figure 28.

Figure 28. Glucose Changes in Adult Pooled, 6-Week, Placebo-Controlled Studies[51]



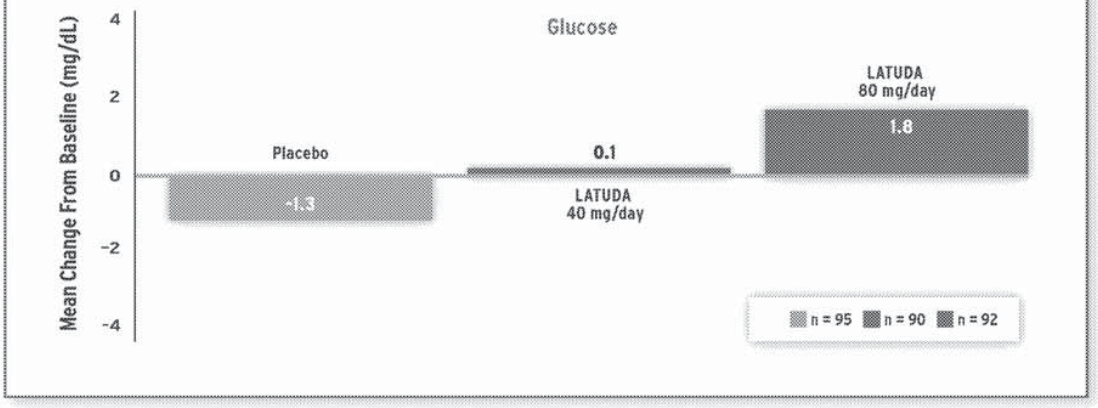
Glucose Changes in Longer-term Uncontrolled Studies in Adults

In the uncontrolled, longer-term (primarily open-label extension) studies, LATUDA was associated with a mean change in glucose of +1.8 mg/dL at Week 24 (n = 355), +0.8 mg/dL at Week 36 (n = 299), and +2.3 mg/dL at Week 52 (n = 307).

Adolescents

In the short-term, placebo-controlled study of adolescents, mean change in fasting serum glucose values were -1.3 for placebo, +0.1 for 40 mg, and +1.8 for 80 mg (Figure 29).[54]

Figure 29. Mean Glucose Change in Adolescents From Baseline to Week 6 (LOCF)[51]



Abbreviation: LOCF, last observation carried forward.

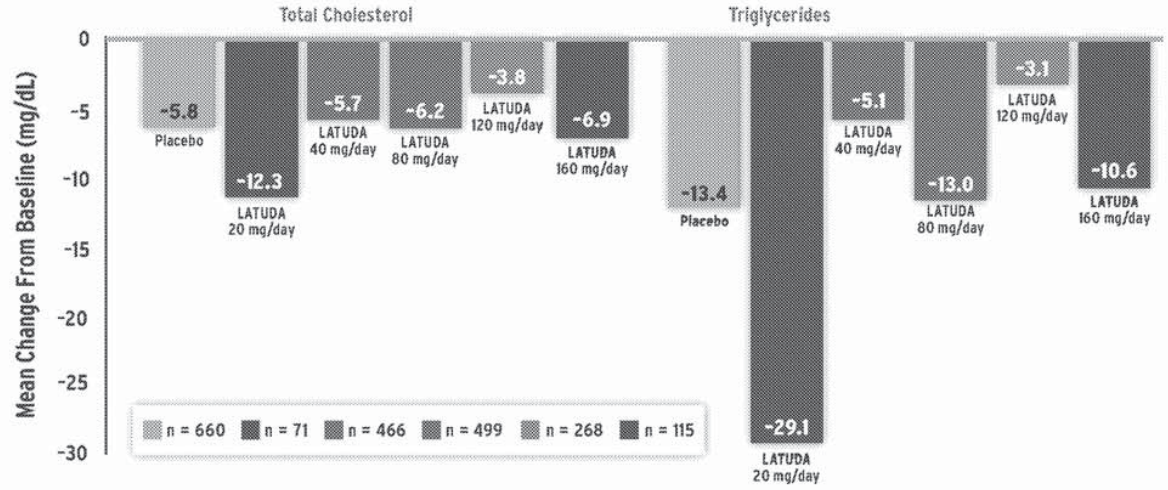
Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Changes in Total Cholesterol and Triglycerides

Adults

Changes in total cholesterol and triglyceride levels observed with LATUDA in pooled 6-week trials in adults are shown in Figure 30.

Figure 30. Lipid Changes in Adult Pooled, 6-Week, Placebo-Controlled Studies[51]



Lipid Changes in Longer-term Uncontrolled Studies in Adults

In the uncontrolled, longer-term (primarily open-label extension) studies, LATUDA was associated with a mean change in total cholesterol and triglycerides of -3.8 (n = 356) and -15.1 (n = 357) mg/dL at Week 24, -3.1 (n = 303) and -4.8 (n = 303) mg/dL at Week 36, and -2.5 (n = 307) and -6.9 (n = 307) mg/dL at Week 52, respectively.

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

IMPORTANT SAFETY INFORMATION FOR LATUDA

Metabolic Changes: Atypical antipsychotic drugs have caused metabolic changes including:

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

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

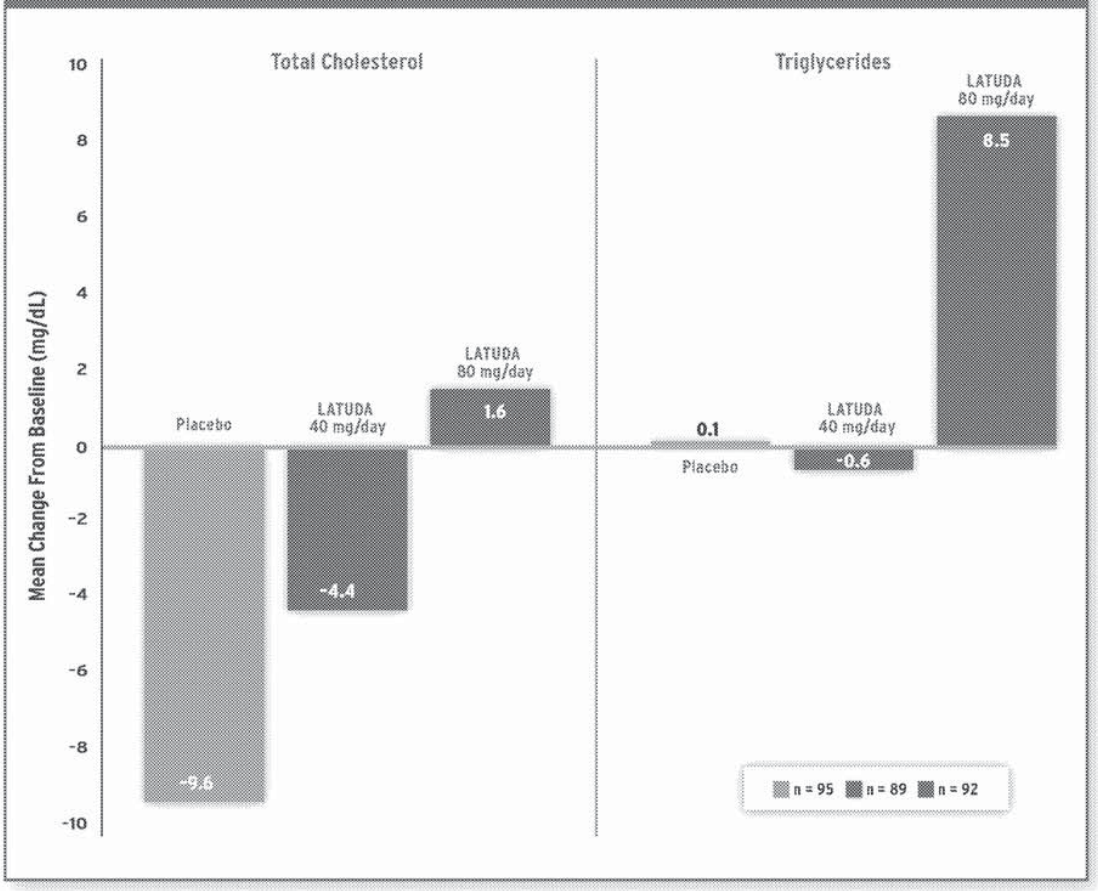
Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Latuda®
(lurasidone HCl) tablets
20mg | 40mg | 60mg | 80mg | 120mg

Adolescents

Changes in total cholesterol and triglyceride levels observed with LATUDA in the short-term, placebo-controlled study with adolescents are shown in Figure 31.

Figure 31. Mean Lipid Changes in Adolescents From Baseline to Week 6 (LOCF)[51]



Abbreviation: LOCF, last observation carried forward.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Changes in Weight

Adults

Mean weight change by LATUDA dose in the pooled short-term studies in adults is shown in Table 22.

Table 22. Mean Change in Weight by Dose in Adult Pooled, 6-Week, Placebo-Controlled Studies[51]

LATUDA 20 mg (n = 71)	LATUDA 40 mg (n = 484)	LATUDA 80 mg (n = 526)	LATUDA 120 mg (n = 291)	LATUDA 160 mg (n = 114)	Placebo (n = 696)
-0.15 kg (-0.33 lb)	0.22 kg (0.49 lb)	0.54 kg (1.19 lb)	0.68 kg (1.50 lb)	0.60 kg (1.32 lb)	-0.02 kg (-0.04 lb)

In pooled short-term trials, the mean weight gain was 0.43 kg (0.95 lb) for LATUDA-treated patients compared with a weight loss of 0.02 kg (0.04 lb) for placebo-treated patients.

In Study 3, mean change in weight from baseline for olanzapine was 4.15 kg (9.15 lb).[58] In Study 5, mean change in weight from baseline for quetiapine XR was 2.09 kg (4.61 lb). [61]

The proportion of patients with a ≥7% increase in body weight at the end of the studies was 4.8% for LATUDA-treated patients versus 3.3% for placebo-treated patients.

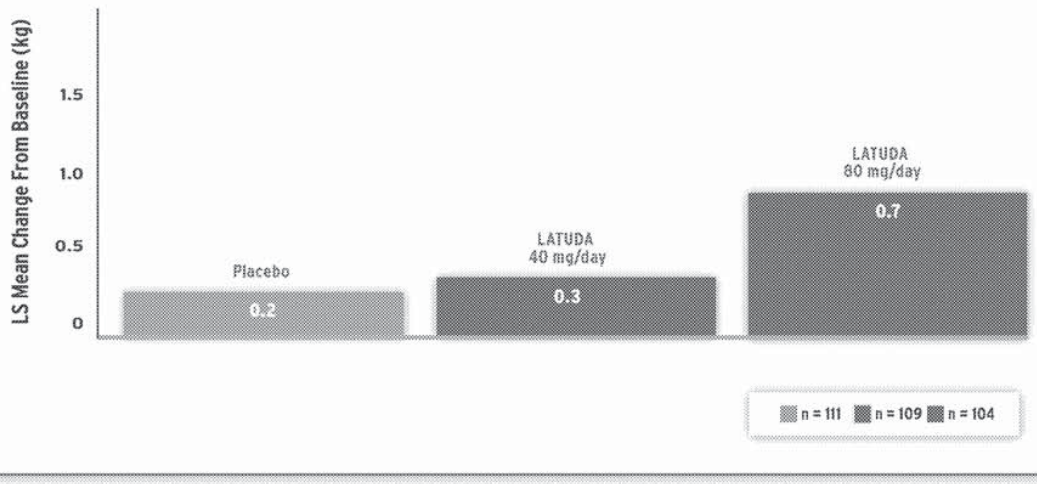
Weight Changes in Longer-term Uncontrolled Studies in Adults

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.69 kg at Week 24 (n = 755), -0.59 kg at Week 36 (n = 443), and -0.73 kg at Week 52 (n = 377).

Adolescents

The proportion of adolescent patients with ≥7% weight gain (at endpoint) was 3.3% with LATUDA vs 4.5% with placebo. Mean weight change from baseline to Week 6 is shown in Figure 32: an increase of 0.2 kg with placebo, an increase of 0.3 kg with LATUDA 40 mg/day, and an increase of 0.7 kg with LATUDA 80 mg/day.

Figure 32. Mean Weight Change in Adolescents From Baseline to Week 6 (LOCF)[51]



Abbreviation: LOCF, last observation carried forward.

Changes in Prolactin

Adults

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was 0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was 0.5 ng/mL and for females was -0.2 ng/mL.

The proportion of patients with prolactin elevations ≥5x ULN was 2.8% for LATUDA-treated patients versus 1.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5x ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 1.6% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -0.9 ng/mL at Week 24 (n = 357), -5.3 ng/mL at Week 36 (n = 190), and -2.2 ng/mL at Week 52 (n = 307).

Adolescents

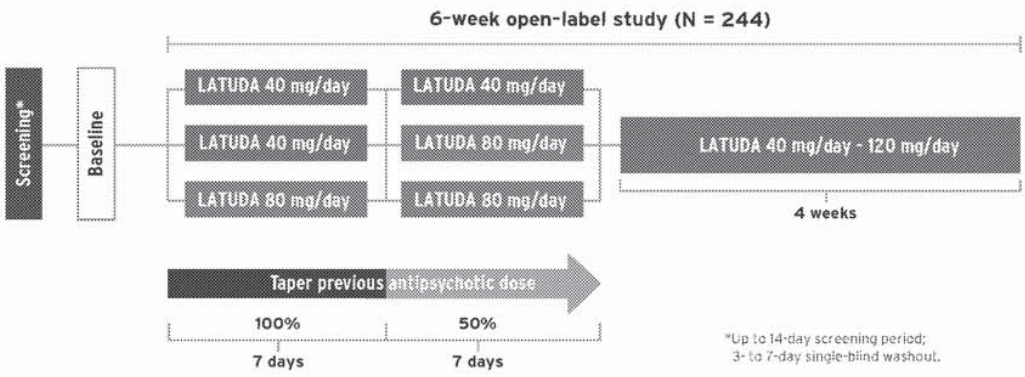
In the short-term, placebo-controlled adolescent study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +1.1 ng/mL and was +0.1 ng/mL for placebo-treated patients. For LATUDA-treated patients, the median change from baseline to endpoint for males was +1.0 ng/mL and for females was +2.6 ng/mL.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Open-label Study Evaluating 3 Dosing Strategies for Switching to LATUDA

This 6-week, open-label study (McEvoy JP, et al; 2013) in adults was designed to evaluate the safety and effectiveness of switching clinically stable but symptomatic outpatients with schizophrenia (N = 244) from their previous antipsychotic to LATUDA. The study design is based on a cross-tapering approach (Figure 33).[63,64]

Figure 33. Open-label Switch Study Design (Adult Patients)[64]



Study patients were switched from a variety of antipsychotic agents: quetiapine (25.8%), risperidone (21.3%), aripiprazole (18.3%), ziprasidone (11.3%), olanzapine (10.0%), paliperidone (3.8%), haloperidol (2.5%), iloperidone (1.7%), perphenazine (1.7%), fluphenazine (1.3%), chlorpromazine (1.3%), asenapine (0.8%), or thiothixene (0.4%).

There were 3 dosing strategies evaluated in the open-label Switch Study. During the first week, the dose of previous (switched-from) antipsychotics was maintained, and treatment with fixed daily doses of LATUDA (either 40 mg or 80 mg) was initiated. For the second week, the dose of the previous antipsychotic was reduced by 50% and LATUDA dosage was either maintained (40 mg/day → 40 mg/day, and 80 mg/day → 80 mg/day) or increased (40 mg/day → 80 mg/day).

All previous antipsychotics were discontinued completely at the end of Week 2 and patients were treated with flexible doses of LATUDA (40-120 mg/day) taken in the evening within 30 minutes after eating.

Primary outcome was treatment failure defined as discontinuation due to an adverse event, exacerbation of underlying illness, or insufficient clinical response.

Secondary outcomes included the following assessments: safety and tolerability, PANSS total score, and CGI-S score.

Results From the Open-label Switch Study

Overall, 82.5% (198/240) of patients (all adults) treated with LATUDA completed treatment in the open-label Switch Study. An additional 4 patients were randomized, but never received treatment.[64]

For the primary endpoint, overall treatment failure with LATUDA was 7.9% (1.3% due to insufficient clinical response, 6.7% due to adverse events [1.7% of adverse events were due to exacerbation of underlying disease]) (Figure 34).[64] Three and eight-tenths percent (3.8%) of patients were lost to follow-up and 5.8% for other reasons including protocol violation, noncompliance, administrative reason, investigator decision, and withdrew consent.

Figure 34. Completion Rate and Treatment Failure Rate Among Patients (Adults) Receiving LATUDA at Week 6 (n = 240)*†[64]

*Four patients were randomized, but exited the study before receiving LATUDA.
†Other includes: protocol violation, noncompliance, administrative reason, investigator decision, withdrew consent.

Rates of discontinuation due to treatment failure were similar between the dosing groups (Table 23).[63]

Table 23. Rates of Discontinuation Due to Treatment Failure by Dosing Group in the Open-label Switch Study[63]

All LATUDA	**7.9% (19/240)**
LATUDA 40/40	6.9% (5/72)
LATUDA 40/80	9.2% (8/87)
LATUDA 80/80	7.4% (6/81)

There were no clinically meaningful differences in time to treatment failure or all-cause discontinuation based on initial dosing regimen between treatment groups.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

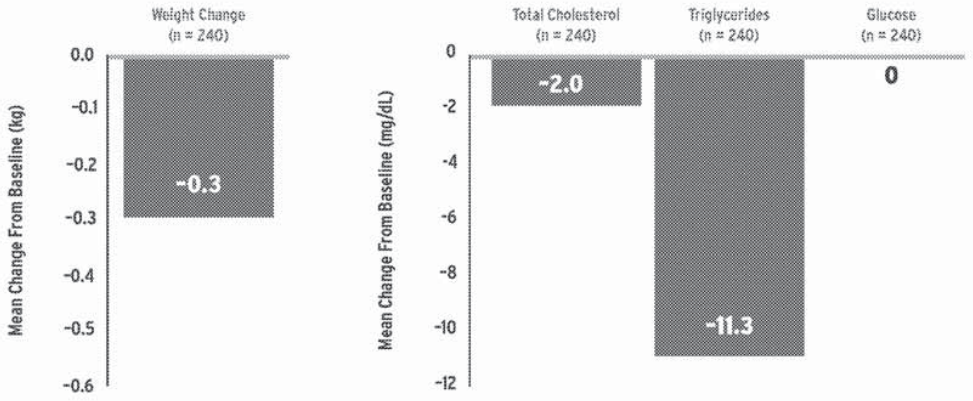
Adverse reactions and changes in metabolic profiles from the open-label Switch Study are summarized in Table 24 and Figure 35, respectively.[63]

Table 24. Adverse Reactions Occurring in ≥5% of All LATUDA Patients (Adults) From the Open-label Switch Study (LOCF)[63]

	LATUDA 40/40 (n = 72)	LATUDA 40/80 (n = 87)	LATUDA 80/80 (n = 81)	All LATUDA (n = 240)
Akathisia	8.3%	14.9%	13.6%	12.5%
Dry mouth	4.2%	10.3%	2.5%	5.8%
Headache	9.7%	11.5%	7.4%	9.6%
Insomnia	4.2%	18.4%	14.8%	12.9%
Nausea	13.9%	9.2%	18.5%	13.8%
Somnolence	9.7%	8.0%	2.5%	6.7%
Vomiting	5.6%	6.9%	8.6%	7.1%

Abbreviation: LOCF, last observation carried forward.

Figure 35. Change in Metabolic Parameters in All LATUDA Patients (Adults) From the Open-label Switch Study (LOCF)[63]



Abbreviation: LOCF, last observation carried forward.

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness.

Changes in Prolactin

Median change from baseline in prolactin through study endpoint after switching to LATUDA was 0.1 ng/mL (n = 240, LOCF).

As with other drugs that antagonize dopamine D_2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

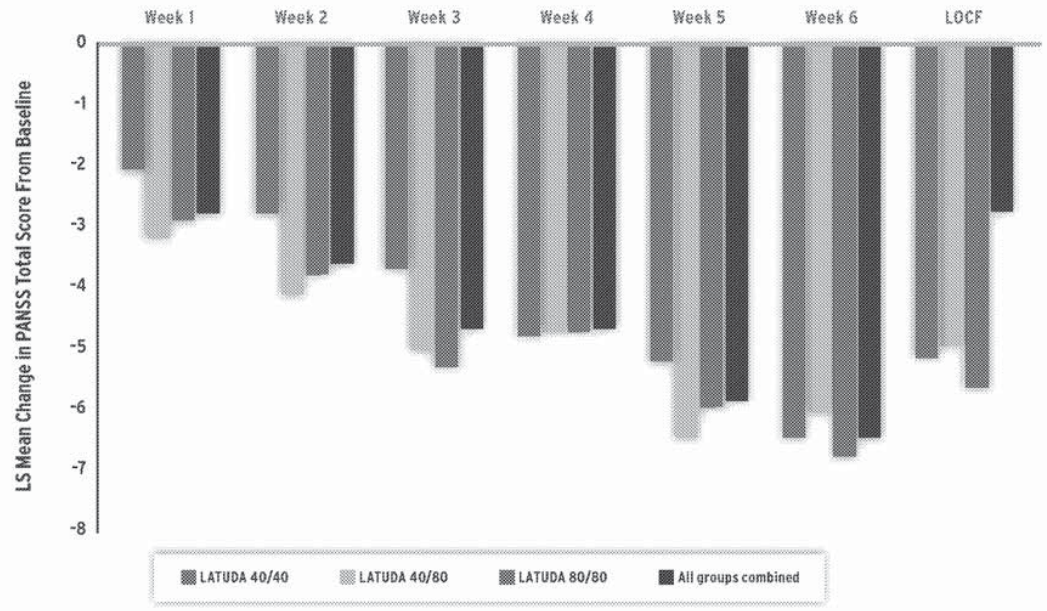
LATUDA improved PANSS total score, a secondary endpoint, at 6 weeks as measured by the mean change from baseline in PANSS total score. Mean baseline PANSS total score for all patients receiving LATUDA was 68.9 (n = 240). LS mean (SE) change in PANSS total score from baseline to LOCF endpoint for all patients receiving LATUDA was -5.3 (0.7) ($P<0.0001$).[63] LS mean change in PANSS total score from baseline at Weeks 1 through 6 and LOCF endpoint is shown in Figure 36 ($P<0.005$ for all dose groups at each week).[63,64]

In addition, LATUDA improved CGI-S score, a secondary endpoint, at 6 weeks as measured by the mean change from baseline in CGI-S score. Mean baseline CGI-S score for all patients receiving LATUDA was 3.7 (n = 240). LS mean (SE) change in CGI-S score from baseline to LOCF endpoint for all patients receiving LATUDA was -0.2 (0.0) ($P<0.0001$).[63]

Results were similar regardless of switch strategy. The switch strategy chosen for an individual patient may be best based on individual needs of the patient and clinical judgment.

Please see additional Important Safety Information, including **Boxed Warnings**, on pages 66-67 and enclosed full Prescribing Information.

Figure 36. Symptom Improvement Measured as LS Mean Change in PANSS Total Scores by LATUDA Dose in the Open-label Switch Study (LOCF) (Adults)[63]



Abbreviations: LOCF, last observation carried forward; LS, least squares; PANSS, Positive and Negative Syndrome Scale.
Baseline PANSS total scores by group: 68.5 for LATUDA 40/40; 68.0 for LATUDA 40/80; 70.2 for LATUDA 80/80; 68.9 for all LATUDA.

Open-label Switch Study Summary

- Similar results were achieved regardless of switch strategy.
  - Switch strategies utilized a gradual cross-taper to switch symptomatic patients from a range of antipsychotics to LATUDA 40 mg/day or 80 mg/day.
- Symptom improvement was seen over the course of the 6-week study.
- The effect of LATUDA on safety parameters was evaluated and the safety profile was consistent with results from controlled 6-week studies in adult patients with schizophrenia.

QTc interval

In a dedicated randomized, double-blind, multiple-dose QT study (N = 43) in adults, patients were treated with LATUDA 120 mg/day or 600 mg/day. The maximum mean (upper 1-sided, 95% confidence interval) increase in baseline-adjusted upper QTc intervals based on individual correction method (QTcI) was 7.5 (11.7) milliseconds and 4.6 (9.5) milliseconds, for the 120 mg and 600 mg dose groups, respectively, as observed 2 to 4 hours after dosing. In this study, no apparent dose/exposure-response relationship was found.[51]

In short-term, placebo-controlled studies, no post-baseline QT prolongations exceeding 500 milliseconds were reported in patients treated with LATUDA or placebo.[51]

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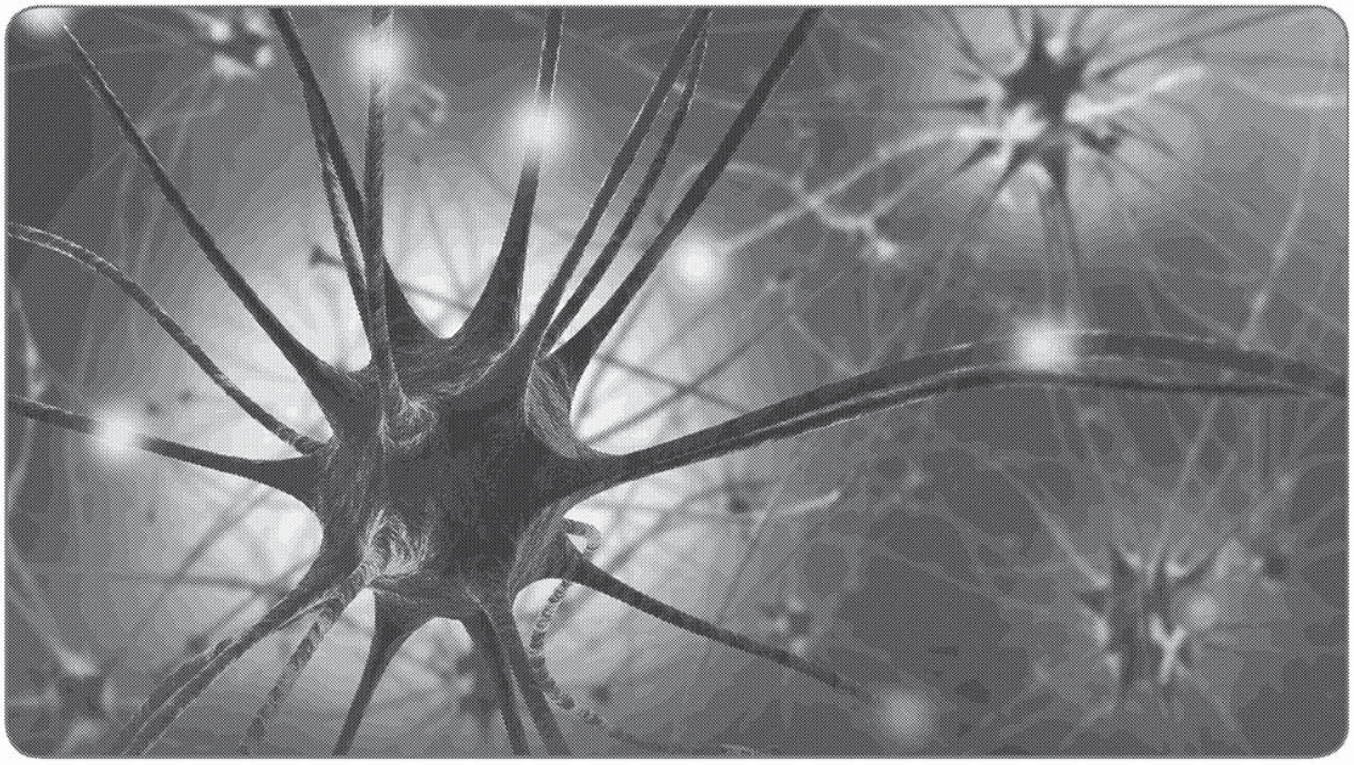

Summary of the Efficacy and Tolerability of LATUDA

- The efficacy of LATUDA was established in one 6-week monotherapy study and one 6-week adjunctive therapy study with lithium or valproate in adult patients with bipolar I disorder (bipolar depression) at doses ranging from 20 mg/day to 120 mg/day.
- The efficacy of LATUDA was established in five 6-week controlled trials of adult patients with acute symptoms of schizophrenia at doses ranging from 40 mg/day to 160 mg/day.
- The efficacy of LATUDA in adolescents with schizophrenia was established in a 6-week study of adolescents (13-17 years) who met DSM-IV-TR criteria for schizophrenia at 2 doses: 40 mg/day and 80 mg/day.
- The safety and tolerability of LATUDA were evaluated in multiple studies.
- LATUDA should be taken with food (at least 350 calories) and no initial dose titration is required.
- The maximum recommended dose is 160 mg/day for adult patients with schizophrenia and 120 mg/day in patients with bipolar depression. The maximum recommended dose is 80 mg/day in adolescents with schizophrenia.

IMPORTANT SAFETY INFORMATION FOR LATUDA

Potential for Cognitive and Motor Impairment: Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

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IMPORTANT SAFETY INFORMATION AND INDICATIONS FOR LATUDA

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

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. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Suicidal Thoughts and Behaviors
Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behavior. LATUDA is not approved for use in pediatric patients with depression.

Contraindications: LATUDA is contraindicated in the following:

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone
- Strong CYP3A4 inhibitors (e.g., ketoconazole)
- Strong CYP3A4 inducers (e.g., rifampin)

Cerebrovascular Adverse Reactions, Including Stroke: In clinical trials, elderly subjects with dementia randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex, reported with administration of antipsychotic drugs. Clinical signs of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage NMS with immediate discontinuation of antipsychotic drugs, including LATUDA, intensive symptomatic treatment, and monitoring.

Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Metabolic Changes: Atypical antipsychotic drugs have caused metabolic changes including:

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

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia/neutropenia has been reported with antipsychotics. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Monitor complete blood count in patients with a pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) or history of drug-induced leukopenia/neutropenia. Discontinue LATUDA at the first sign of a decline in WBC in the absence of other causative factors.

Orthostatic Hypotension and Syncope: Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest at the beginning of treatment and when increasing the dose. Monitor patients vulnerable to hypotension and those with cardiovascular and cerebrovascular disease.

Falls: Antipsychotics may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls causing fractures or other injuries. For patients with disease, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating treatment and recurrently during therapy.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold.

Potential for Cognitive and Motor Impairment: Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

Body Temperature Regulation: Use LATUDA with caution in patients who may experience conditions that increase body temperature (e.g., exercising strenuously, exposure to extreme heat, concomitant medication with anticholinergic activity, or being subject to dehydration).

Dysphagia: Antipsychotics, including LATUDA, have been associated with esophageal dysmotility and aspiration, and should be used with caution in patients at risk for aspiration pneumonia.

MOST COMMONLY OBSERVED ADVERSE REACTIONS

Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo) for LATUDA:

- Adult patients with bipolar depression: akathisia, extrapyramidal symptoms, and somnolence
- Adult patients with schizophrenia: somnolence, akathisia, extrapyramidal symptoms, and nausea
- Adolescent patients (13 to 17 years) with schizophrenia: somnolence, nausea, akathisia, extrapyramidal symptoms (non-akathisia), vomiting, and rhinorrhea/rhinitis

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 877-737-7226 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

INDICATIONS

LATUDA is indicated for:

- Treatment of adult and adolescent patients age 13 to 17 years with schizophrenia
- Treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate in adults

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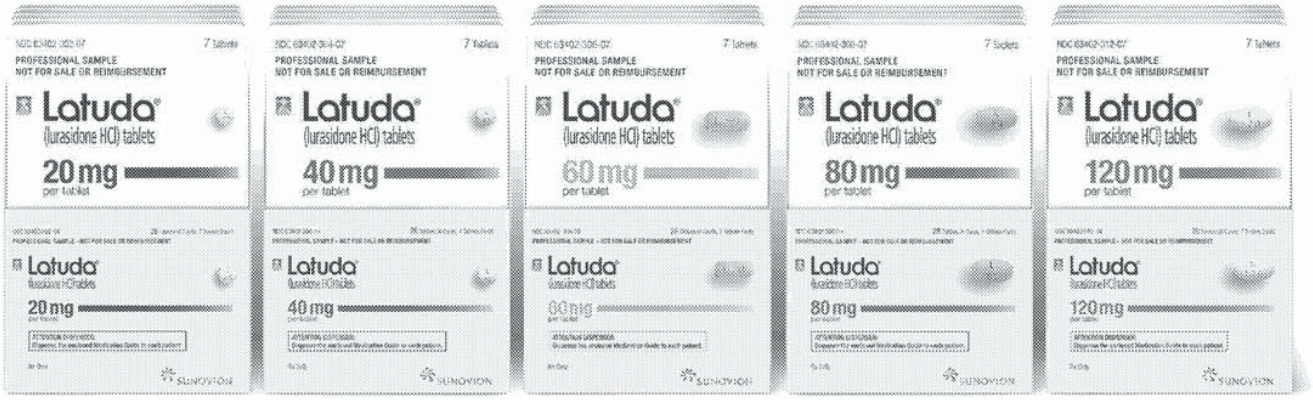

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