What type of patient with schizophrenia is appropriate for LATUDA?
LATUDA is an atypical antipsychotic agent indicated for the treatment of adult and adolescent patients age 13 to 17 years with schizophrenia.

What is LATUDA’s mechanism of action?
The mechanism of action of LATUDA, as with other drugs having efficacy in schizophrenia, is unknown. It has been suggested that the efficacy of LATUDA could be mediated through a combination of central dopamine Type 2 (D₂) and serotonin Type 2 (5-HT₂A) receptor antagonism.

What is LATUDA’s in vitro receptor-binding profile?
LATUDA is an antagonist with high-affinity binding at the dopamine D₂ receptors (Ki=1 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors 5-HT₂A (Ki=0.5 nM) and 5-HT₇ (Ki=0.5 nM) receptors. It also binds with moderate affinity to the human α₂C adrenergic receptors (Ki=11 nM), is a partial agonist at serotonin 5-HT₁A (Ki=6.4 nM) receptors, and is an antagonist at the α₂A adrenergic receptors (Ki=41 nM). LATUDA exhibits little or no affinity for histamine H₁ and muscarinic M₁ receptors (IC₅₀>1,000 nM).

How was the efficacy of LATUDA in schizophrenia established?
In adults with schizophrenia, the efficacy of LATUDA was established in five 6-week, placebo-controlled studies. Study 3 (Meltzer et al) also included an active-control arm (olanzapine 15 mg/day) to assess for assay sensitivity. The study was not designed for comparison of LATUDA to olanzapine. Study 5 (Loebel et al) also included an active-control arm (quetiapine XR 600 mg/day) to assess for assay sensitivity. The study was not designed for comparison of LATUDA to quetiapine XR.

In these pivotal studies, change from baseline to Week 6 endpoint in the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (derived from the PANSS) was the primary efficacy endpoint, and the Clinical Global Impression of Severity scale (CGI-S) was used as key secondary endpoint.

In adolescents with schizophrenia, the efficacy of LATUDA was examined in a 6-week, randomized, double-blind, placebo-controlled, fixed-dose study of 326 subjects aged 13 to 17 years who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, criteria for schizophrenia.

The primary efficacy endpoint was the change from baseline to Week 6 in the PANSS total score, and the key secondary endpoint was the change in CGI-S score over the same time frame.

What is an active-control trial?
According to the FDA Guidance for Industry E10 Choice of Control Group and Related Issues in Clinical Trials, an active-control trial is one in which an investigational drug is compared with a known active drug. The inclusion of an active control in the schizophrenia studies helps to validate assay sensitivity.

What is assay sensitivity?
The FDA Guidance for Industry E10 Choice of Control Group and Related Issues in Clinical Trials states that assay sensitivity is a property of a clinical trial defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment (eg, placebo). Often, an active control is used to establish assay sensitivity.
Where were the studies demonstrating the efficacy of LATUDA in schizophrenia conducted?

Studies 1 (006; Ogasa et al) and 2 (196; Nakamura et al) in the adult population were conducted in the United States, and adult Studies 3 (231; Meltzer et al), 4 (229; Nasrallah et al), and 5 (233; Loebel et al), as well as the adolescent study (301; Goldman et al), were conducted globally (North America, Asia, Europe, and South America).

What is the longer-term efficacy (longer-term data) of LATUDA in patients with schizophrenia?

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. However, a number of uncontrolled, longer-term studies (primarily open-label extension studies) evaluating the safety of LATUDA up to 52 weeks in adults with schizophrenia have been conducted, the results of which are included in the Prescribing Information.

Safety and Tolerability

What were the side effects seen in LATUDA-treated patients with schizophrenia?

**Adults**

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in adult patients with schizophrenia treated with LATUDA were somnolence, akathisia, extrapyramidal symptoms, and nausea. The apparent dose-related adverse reactions were akathisia and extrapyramidal symptoms. In the pooled 6-week trials, 9.5% of patients taking LATUDA discontinued due to adverse reactions versus 9.3% for placebo. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse reactions in ≥2% of LATUDA-treated adult patients and occurring at a greater incidence than in the placebo-treated adult patients in the 6-week schizophrenia trials included nausea, vomiting, dyspepsia, salivary hypersecretion, back pain, somnolence (includes adverse reaction terms: hypersomnia, hypersonolence, sedation, and somnolence), akathisia, extrapyramidal disorder (includes adverse reaction terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus), dizziness, insomnia, agitation, anxiety, and restlessness.

**Adolescents**

Adverse reactions in ≥2% of LATUDA-treated adolescent patients and occurring at a greater incidence than in the placebo-treated adolescent patients in the 6-week schizophrenia trial were somnolence (includes adverse reaction terms: hypersomnia, sedation, and somnolence), nausea, viral infection (includes adverse reaction terms: nasopharyngitis, influenza, viral infection, and upper respiratory tract infection), akathisia, vomiting, dizziness, diarrhea, dry mouth, rhinitis (includes adverse reaction terms: rhinitis, allergic rhinitis, rhinorrhea, and nasal congestion), oropharyngeal pain, and tachycardia.

Overall, twice as many adolescent patients in the placebo group discontinued treatment due to adverse reactions compared with adolescent patients in the combined LATUDA treatment groups (8% vs 4%, respectively).
What was the effect of LATUDA on weight in patients with schizophrenia?

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

**Adults**

In pooled short-term trials, the mean weight change was +0.43 kg for LATUDA-treated adult patients compared to -0.02 kg for placebo-treated adult patients. In Study 3 (231; Meltzer et al), at Week 6 (study endpoint), mean weight gain with olanzapine 15 mg/day was 4.15 kg. In Study 5 (233; Loebel et al), mean weight gain with quetiapine XR 600 mg/day was 2.09 kg. The proportion of patients with clinically significant weight gain (≥7%) was 4.8% for LATUDA versus 3.3% for placebo.

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**

In the 6-week schizophrenia trial in adolescents, the mean weight gain was 0.5 kg for LATUDA-treated patients compared to 0.2 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight was 3.3% for LATUDA versus 4.5% for placebo.

What was the effect of LATUDA on total cholesterol and triglyceride levels in patients with schizophrenia?

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

**Adults**

In pooled short-term trials, the mean change from baseline for total cholesterol by dose was -12.3 mg/dL for LATUDA 20 mg/day, -5.7 mg/dL for LATUDA 40 mg/day, -6.2 mg/dL for LATUDA 80 mg/day, -3.8 mg/dL for LATUDA 120 mg/day, and -5.9 mg/dL for LATUDA 160 mg/day versus -5.8 mg/dL for placebo. In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies) in adults, LATUDA was associated with a mean change in total cholesterol of -3.8 mg/dL (n=356) at Week 24, -3.1 mg/dL (n=303) at Week 36, and -2.5 mg/dL (n=307) at Week 52.

In pooled short-term trials, the mean change from baseline for triglycerides was -29.1 mg/dL for LATUDA 20 mg/day, -5.1 mg/dL for LATUDA 40 mg/day, -13.0 mg/dL for LATUDA 80 mg/day, -3.1 mg/dL for LATUDA 120 mg/day, and -10.6 mg/dL for LATUDA 160 mg/day versus -13.4 mg/dL for placebo. In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies) in adults, LATUDA was associated with a mean change in triglycerides of -15.1 mg/dL (n=357) at Week 24, -4.8 mg/dL (n=303) at Week 36, and -6.9 mg/dL (n=307) at Week 52.

**Adolescents**

In the schizophrenia study in adolescents, the mean change from baseline to the 6-week endpoint in fasting total cholesterol was -4.4 for LATUDA 40 mg/day, +1.5 for LATUDA 80 mg/day, and -9.6 for placebo. The mean change from baseline in fasting triglycerides was -0.6 for LATUDA 40 mg/day, +8.5 for LATUDA 80 mg/day, and +0.1 for placebo.
What was the effect of LATUDA on glucose levels in patients with schizophrenia?

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

**Adults**

In pooled short-term trials in adults, the mean change from baseline in glucose by dose was -0.6 mg/dL for LATUDA 20 mg/day, +2.6 mg/dL for LATUDA 40 mg/day, -0.4 mg/dL for LATUDA 80 mg/day, +2.5 mg/dL for LATUDA 120 mg/day, and +2.5 mg/dL for LATUDA 160 mg/day versus -0.0 mg/dL for placebo.

In the uncontrolled, longer-term schizophrenia studies (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 6-week schizophrenia trial in adolescents, the mean change from baseline in fasting glucose was +0.1 for LATUDA 40 mg, +1.8 for LATUDA 80 mg, and -1.3 for placebo.

What was the effect of LATUDA on prolactin levels in patients with schizophrenia?

As with other drugs that antagonize D2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

**Adults**

In the pooled short-term studies in adults, the median change from baseline to endpoint in prolactin levels in LATUDA-treated patients was +0.4 ng/mL and -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint in females was -0.2 ng/mL and +0.5 ng/mL in males. The overall median change in prolactin levels by dose was -1.1 ng/mL for LATUDA 20 mg/day, -1.4 ng/mL for LATUDA 40 mg/day, -0.2 ng/mL for LATUDA 80 mg/day, +3.3 ng/mL for LATUDA 120 mg/day, and +3.3 ng/mL for LATUDA 160 mg/day versus -1.9 ng/mL for placebo. In the uncontrolled longer-term 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 schizophrenia study in adolescents, the median increase from baseline to endpoint in prolactin levels for LATUDA-treated patients was 1.1 ng/mL and 0.1 ng/mL for placebo-treated patients. For LATUDA-treated patients, the median change from baseline to endpoint was +2.6 ng/mL in females and +1.0 ng/mL in males. The overall median change in prolactin levels by dose was +0.75 ng/mL for LATUDA 40 mg/day, +1.20 ng/mL for LATUDA 80 mg/day, and +0.10 ng/mL for placebo.

How significant of a problem is akathisia in adult patients with schizophrenia when taking LATUDA?

Based on the pooled data from short-term, placebo-controlled studies in adults, the apparent dose-related adverse reactions were akathisia and extrapyramidal symptoms. The frequency of akathisia increased with doses up to 120 mg/day. Akathisia was reported in 5.6% of patients who received LATUDA 20 mg/day, 10.7% with LATUDA 40 mg/day, 12.3% with LATUDA 80 mg/day, 22.0% with LATUDA 120 mg/day and 7.4% of patients receiving LATUDA 160 mg/day. Akathisia was reported in 3% of patients receiving placebo. Discontinuation due to akathisia was reported in 1.4% of LATUDA-treated patients versus 0% of placebo-treated patients.
Dosing and Administration

What is the dosing of LATUDA for patients with schizophrenia?

In adult and adolescent patients, LATUDA 40 mg/day is the recommended starting dose, and initial dose titration is not required. LATUDA has been shown to be effective in adults in a dose range of 40 mg/day to 160 mg/day, with a maximum recommended dose of 160 mg/day. In adolescents, LATUDA has been shown to be effective in a dose range of 40 mg/day to 80 mg/day, with a maximum recommended dose of 80 mg/day.

Dose adjustment is recommended in moderate (creatinine clearance: 30 to <50 mL/min) and severe (creatinine clearance: <30 mL/min) renal impairment patients. For these patients, the recommended starting dose is 20 mg/day, and the dose should not exceed 80 mg/day. In patients with moderate (Child-Pugh Score = 7 to 9) or severe (Child-Pugh Score = 10 to 15) hepatic impairment, the recommended LATUDA 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.

LATUDA should not be used with a strong CYP3A4 inhibitor (eg, ketoconazole) or inducer (eg, rifampin). If LATUDA is being prescribed and a moderate CYP3A4 inhibitor (eg, diltiazem) 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. 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.

Does taking LATUDA with or without food make a difference?

Yes. 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 the C_max approximately 3-fold, compared with fasting conditions. LATUDA exposure was not affected as the meal size was increased from 350 to 1000 calories, and was independent of meal fat content. In the clinical studies, LATUDA was administered with food.

Antipsychotic Switching

How do I switch my patient with schizophrenia from another antipsychotic agent to LATUDA?

McEvoy and colleagues conducted a 6-week, open-label study in adult patients to evaluate strategies for switching from other antipsychotics to LATUDA. This study was published in McEvoy JP, Citrome L, Hernandez D, Cucchiaro J, Hsu J, Pikalov A, Loebel A. Effectiveness of Lurasidone in Patients with Schizophrenia or Schizoaffective Disorder Switched From Other Antipsychotics: A Randomized, 6-Week, Open-label Study. J Clin Psychiatry. 2013;74(2):170-179.

Use your clinical judgment when transitioning patients from their current medications. As a reminder, initial dose titration is not required with LATUDA. The recommended starting dose of LATUDA is 40 mg/day, which is also a therapeutic dose.