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ADIS DRUG Q&A

Lurasidone in schizophrenia in adolescents: a profile of its use

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Abstract

The second-generation (atypical) antipsychotic lurasidone (Latuda®) presents a useful option to consider for the treatment of schizophrenia in adolescents. As demonstrated in a 6-week, randomised, double-blind, placebo-controlled phase 3 clinical trial, oral lurasidone provides clinically meaningful symptom improvements in adolescents with schizophrenia. Furthermore, continued improvement in symptoms is observed during longer-term treatment, based on a 2-year open-label extension study. The drug is generally well tolerated and appears to have a low propensity for weight gain and other metabolic adverse events commonly associated with second-generation antipsychotics, a potential advantage that may be particularly relevant to adolescent patients.

Plain Language Summary

Although second-generation antipsychotic medications are generally considered to have improved tolerability compared with first-generation antipsychotics, they are commonly associated with a risk of weight gain and other metabolic adverse effects. Lurasidone (Latuda®) is a second-generation antipsychotic which, relative to some other antipsychotics, appears to have a favourable tolerability profile in terms of metabolic effects, which could be particularly beneficial in adolescent patients. As demonstrated in a 6-week clinical trial, lurasidone provides clinically meaningful symptom improvements in adolescents with schizophrenia compared with placebo. Furthermore, continued improvement in symptoms is observed during longer-term treatment. The drug is generally well tolerated; minimal changes in metabolic parameters were observed in patients over 2 years of treatment. In conclusion, lurasidone is effective and generally well tolerated in the treatment of schizophrenia in adolescents and, having a low propensity for weight gain and other metabolic adverse effects, presents a useful treatment option to consider.

Digital Features for this Adis Drug Q&A can be found at https://doi.org/10.6084/m9.figshare.14863449.

What is the rationale for using lurasidone in schizophrenia in adolescents?

Lurasidone (Latuda®) is an established second-generation (atypical) antipsychotic agent which has been approved for use in the treatment of schizophrenia in adults since 2010 in the USA [1] and since 2014 in the EU [2]. Subsequent to further clinical evaluation, the approvals for the use of lurasidone in the treatment of schizophrenia were expanded (in 2017 in the USA and in 2020 in the EU) to include use in adolescents aged 13–17 years.

There is a multitude of antipsychotic agents available for use in the treatment of schizophrenia, including several second-generation antipsychotics besides lurasidone (e.g. aripiprazole, olanzapine, paliperidone, quetiapine, risperidone) that are approved by various regulatory authorities for use in adolescents [3]. Given their broadly similar efficacies, the choice of agent used for the treatment of schizophrenia is commonly guided by the tolerability profiles of the individual agents [4]. Although largely based on data from adults, relative to some other agents of the same class, lurasidone appears to have a favourable tolerability profile in terms of a low risk for weight gain and metabolic effects [4–6]. Such tolerability benefits may have particular relevance for adolescents with schizophrenia, given the long-term health risks associated with weight gain and other metabolic adverse events in adolescence [7].

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Adis evaluation of lurasidone in the treatment of schizophrenia in adolescents
Second-generation antipsychotic indicated for the treatment of schizophrenia in individuals aged ≥ 13 years
Provides clinically meaningful improvements in symptoms of schizophrenia in the acute setting relative to placebo
Continued improvement in symptoms is observed during longer-term treatment
Generally well tolerated
Appears to have a low propensity for weight gain and other metabolic adverse events

This article provides an evidence-based, narrative review of the pharmacological properties, efficacy, tolerability and clinical use of lurasidone in adolescents (aged 13–17 years) with schizophrenia, with a focus on use of the agent under the EU label. Use of lurasidone in schizophrenia in adults, or in depressive episode associated with Bipolar I Disorder (which is approved in the USA), is outside the scope of the current article. Unless otherwise indicated, lurasidone doses provided in this article refer to lurasidone hydrochloride, with doses of 20, 40, 60 and 80 mg being equivalent to 18.5, 37, 55.5 and 74 mg of lurasidone itself (i.e. without the hydrochloride salt).

How should lurasidone be used in adolescents?

A summary of the EU Summary of Product Characteristics for use of lurasidone in the treatment of schizophrenia in adolescents is provided in Table 1. Details of clinically relevant drug (and other) interactions which may potentially occur with lurasidone are provided in Table 2.

For use in adolescents, lurasidone should be prescribed by an expert in paediatric psychiatry [2]. Patients should be closely monitored during the first few days to weeks after treatment initiation given that, during antipsychotic treatment, improvement in the patient's clinical condition may take time. Supervision by a clinician is also needed when switching between antipsychotic medications. Lurasidone should not be used during pregnancy unless clearly necessary [2].

Prior to starting antipsychotic medications (particularly second-generation agents), treatment guidelines for adolescents recommend that the patient's and/or family history of obesity, diabetes, cardiovascular disease, dyslipidaemia or hypertension be noted [8, 9]. Other recommended investigations to be performed at baseline include bodyweight, body mass index (BMI), waist circumference, blood pressure, fasting blood glucose, blood lipid profile and assessment for the presence of any movement disorders or extrapyramidal symptoms (EPS). Bodyweight and BMI should continue to be monitored regularly, particularly within the first 12 weeks of starting treatment. Blood pressure, fasting blood glucose and the blood lipid profile should be assessed again at 12 weeks. Bodyweight, BMI, waist circumference, blood pressure, fasting blood glucose and the blood lipid profile should then continue to be monitored regularly (every 3–12 months) during treatment. Monitoring for the presence of EPS should also be performed regularly, especially during titration [8, 9].

How does lurasidone work?

Although the precise mechanism of action has not been determined, the therapeutic efficacy of lurasidone in schizophrenia is believed to involve the antagonism of dopamine D_2 and serotonin 5-HT_{2A} receptors [1, 2]. Lurasidone binds to D_2, 5-HT_{2A} and 5-HT_7 receptors with high affinity (Ki values of 0.994, 0.47 and 0.495 nM, respectively) [2]. Lurasidone also antagonises α2c-adrenergic receptors and α2a-adrenergic receptors with moderate binding affinity (Ki values of 10.8 and 40.7 nM, respectively) and exhibits partial agonism at the 5-HT_{1A} receptor (Ki = 6.38 nM). Lurasidone has only weak affinity for the 5-HT_{2C} receptor and the affinity for histaminergic or muscarinic receptors is negligible [10]. The minimal activity of lurasidone at 5-HT_{2C} and histamine H1 receptors may contribute to the favourable tolerability profile of lurasidone in terms of a low risk for weight gain and metabolic effects [7, 11].

More detailed information on the pharmacodynamics of lurasidone is available from earlier reviews of the drug [6, 12].

What are the pharmacokinetic properties of lurasidone?

Data in this section are primarily drawn from studies in adults, but pharmacokinetic data available from 281 paediatric patients aged 6–17 years (including 234 adolescents aged 13–17 years) demonstrate that lurasidone exposure in paediatric patients is generally similar to that observed in adults [2]. Further, available data include a pharmacokinetic study in 105 paediatric patients with psychiatric disorders, which found that exposure to lurasidone and its active metabolites

Table 1 Summary of the prescribing information of lurasidone in schizophrenia in adolescents in the EU [2]

What is the approved indication for lurasidone?	
The treatment of schizophrenia in individuals aged ≥ 13 years	
How is lurasidone available?	
As film-coated tablets at doses of 18.5 mg, 37 mg and 74 mg	
How should lurasidone be administered?	
Tablets should be taken orally (swallowed whole) once daily (at the same time each day) with a meal	
The recommended starting dose is 37 mg; no initial dose titration is required	
The dose can be increased (based on physician judgement and observed clinical response) to a maximum daily dose in adolescents of 74 mg	
When used concomitantly with moderate CYP3A4 inhibitors, reduce the starting dose to 18.5 mg	
Dose adjustment may be necessary when used concomitantly with mild or moderate CYP3A4 inducers (see Table 2)	
What are the contraindications to the use of lurasidone?	
Concomitant administration of strong CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) and strong CYP3A4 inducers [e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St John's wort (*Hypericum perforatum*)]	
Hypersensitivity to lurasidone or any of the excipients	
How should lurasidone be used in special populations?	
Renal impairment	Mild: no adjustment required
	Moderate or severe, or ESRD: recommended starting dose is 18.5 mg
	ESRD: should only be used if potential benefits outweigh potential risks; clinical monitoring is advised
Hepatic impairment	Mild: no adjustment required
	Moderate: recommended starting dose is 18.5 mg
	Severe: recommended starting dose is 18.5 mg; maximum daily dose should not exceed 37 mg
What other special warnings/precautions pertain to the use of the lurasidone?[a]	
Suicidality	Closely supervise high-risk patients under antipsychotic therapy
Tardive dyskinesia	Consider discontinuation of all antipsychotics if signs and symptoms appear
Cardiovascular disorders/QT prolongation	Exercise caution when lurasidone is prescribed in patients with known cardiovascular disease or family history of QT prolongation, or hypokalaemia, and in concomitant use with other medicinal products thought to prolong the QT interval
Seizures	Use lurasidone cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold
Neuroleptic malignant syndrome	Discontinue lurasidone if neuroleptic malignant syndrome is suspected
Venous thromboembolism	Identify all possible risk factors for venous thromboembolism before and during treatment with lurasidone and undertake preventive measures
Hyperprolactinaemia	Counsel patients on signs and symptoms of elevated prolactin and advise to seek medical attention if any signs and symptoms are experienced
Weight gain	Clinical monitoring of weight is recommended
Hyperglycaemia	Clinically monitor diabetic patients and patients with risk factors for the development of diabetes mellitus
Orthostatic hypotension/syncope	Consider monitoring of orthostatic vital signs in patients who are vulnerable to hypotension

Lurasidone doses of 18.5 mg, 37 mg and 74 mg mentioned in this table are equivalent to lurasidone hydrochloride doses of 20 mg, 40 mg and 80 mg, respectively, used elsewhere in this article

ESRD end-stage renal disease

[a]Consult local prescribing information for full details on warnings and precautions pertaining to the use of lurasidone, including on some further warnings that may or may not be relevant to use in adolescents

is dose-proportional over the dose range of 20–160 mg/day [13].

Lurasidone is to be taken with food (as was done in the pivotal clinical trials), which increases lurasidone exposure approximately two- to three-fold compared with when the drug is administered under fasting conditions [2]. Peak serum concentrations of lurasidone are reached ~ 1–3 h after administration. Steady-state pharmacokinetics are reached within 7 days of starting once-daily lurasidone. Lurasidone has a mean apparent volume of distribution of ~ 6000 L following administration of a 40-mg dose, indicating wide distribution in tissues. The drug is highly (~ 99%) bound by serum proteins.

Lurasidone metabolism primarily occurs via CYP3A4, leading to the production of four main metabolites (two active, two non-active) [2]. Lurasidone and one of the active metabolites (ID-14283) are most responsible for the pharmacodynamic effects of the drug. Lurasidone has an elimination half-life of 20–40 h. Following administration of a radiolabelled dose, ~ 86% of radioactivity was recovered, 67% in faeces and 19% (mostly as metabolites) in urine.

Table 2 Clinically relevant drug (and other) interactions which may potentially occur with lurasidone [2]

Potential interacting substance(s)	Potential effect and/or recommended action
Other centrally acting medicinal products; alcohol	Use caution
Medicinal products that prolong the QT interval	Use caution
CYP3A4 inhibitors	Can increase exposure to lurasidone; concomitant use of strong CYP3A4 inhibitors is contraindicated
CYP3A4 inducers	Can decrease exposure to lurasidone; concomitant use of strong CYP3A4 inducers is contraindicated; carefully monitor patients receiving concomitant mild or moderate CYP3A4 inducers and adjust lurasidone dose if necessary
P-gp and BCRP transporter inhibitors	May increase exposure to lurasidone
CYP3A4 substrates with a narrow therapeutic index	May increase exposure to the coadministered CYP3A4 substrate; monitoring is recommended
BCRP substrates	May increase exposure to the coadministered BCRP substrate; monitoring is recommended
Grapefruit juice	Instruct patients to avoid grapefruit juice during treatment

BCRP breast cancer resistance protein, *P-gp* P-glycoprotein

Exposure to lurasidone is increased in individuals with hepatic or renal impairment and dose adjustments may be necessary (Table 1). Based on population pharmacokinetic analysis, no dose adjustments are required based on gender or race (although lurasidone exposure is ~ 1.5 fold higher in Asians compared with Caucasians) [2].

What is the efficacy of lurasidone in schizophrenia in adolescents?

Lurasidone provides clinically meaningful symptom improvements in adolescents with schizophrenia, based on the results of a 6-week, double-blind, multinational phase 3 trial in which patients were randomised to fixed doses of lurasidone 40 or 80 mg/day or placebo (Fig. 1) [14]. Furthermore, results from a 2-year, open-label extension study in which patients received flexibly dosed lurasidone 20, 40, 60 or 80 mg/day demonstrate that longer-term treatment

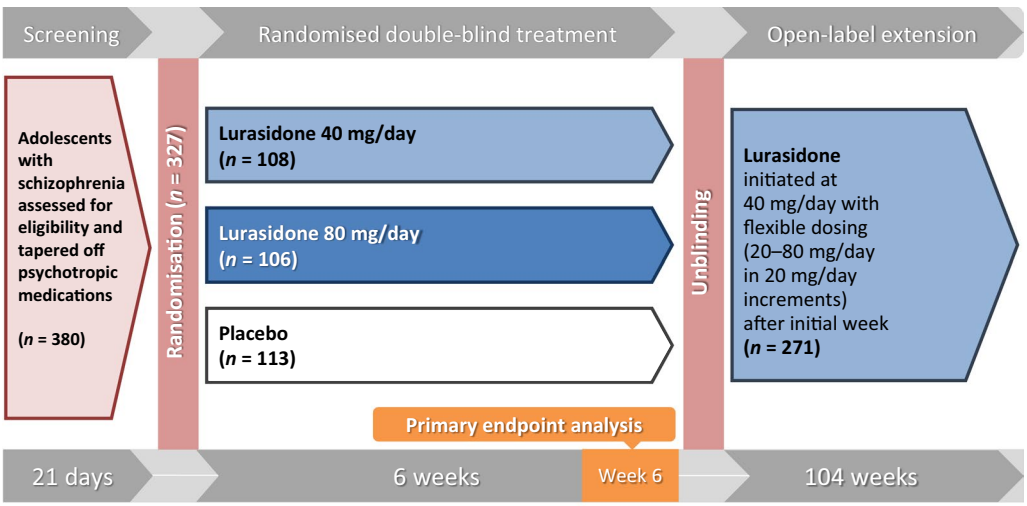

Fig. 1 Design of the randomised, double-blind, placebo-controlled multinational phase 3 trial [14] and open-label extension study [11] evaluating lurasidone in adolescents (aged 13–17 years) with schizophrenia. Primary endpoint and final analysis results are reported in the animated figure (available online). Patients randomised to lurasidone 80 mg/day received lurasidone 40 mg/day for days 1–3 and lurasidone 80 mg/day from day 4 onward. One patient randomised to placebo did not receive study medication and is not included in efficacy analyses. *LSM* least-squares mean, *PANSS* Positive and Negative Syndrome Scale

with lurasidone is associated with continued improvement in schizophrenia symptoms in adolescents [11].

Participants in the 6-week trial were aged 13–17 years, had a diagnosis of schizophrenia and were experiencing an acute exacerbation of disease that was ≤2 months in duration, and had a Positive and Negative Syndrome Scale (PANSS) total score ≥70 and ≤120 and a Clinical Global Impressions-Severity (CGI-S) score ≥4 [14]. Across treatment groups, patients had a mean age of 15.3–15.5 years, a mean age at psychosis symptom onset of 12.9–13.4 years, a mean PANSS total score of 92.8–94.5 and a mean CGI-S score of 4.8–4.9. Sixty-four percent of patients were male, 53% had one or more prior hospitalisations and 83% had prior use of antipsychotic medication.

In both lurasidone treatment groups, the least-squares mean (LSM) change from baseline to week 6 in PANSS total score (primary endpoint) was significantly greater than in the placebo group (Table 3). Significant ($p < 0.05$) separation from placebo on the PANSS total score was observed at week 1 for both lurasidone treatment groups and continued at all subsequent visits [14]. LSM changes in PANSS scores from baseline to week 6 were also significantly ($p < 0.05$) greater in lurasidone 40 mg/day recipients and lurasidone 80 mg/day recipients versus placebo recipients for each of the PANSS positive, negative, general psychopathology and excitability subscale scores. In the key secondary endpoint, the LSM change from baseline to week 6 in CGI-S score was also significantly greater in both lurasidone treatment groups than in the placebo group (Table 3). Significant ($p < 0.05$) separation from placebo on CGI-S score was observed from week 1 for the lurasidone 40 mg/day group and from week 4 for the lurasidone 80 mg/day group. Responder rates (defined as achieving a ≥20% reduction in PANSS total score from baseline to week 6, last observation carried forward) were also significantly ($p < 0.001$) higher in lurasidone 40 mg/day recipients (63.9%) and lurasidone 80 mg/day recipients (65.1%) versus placebo recipients (42.0%).

Of the 285 patients who completed the 6-week double-blind trial, 271 (95.1%) continued into the open-label extension study, including 90 patients who received lurasidone 40 mg/day in the double-blind trial, 91 who received lurasidone 80 mg/day and 90 who received placebo [11]. Regardless of their prior treatment assignment, all patients who were enrolled in the extension study were started on lurasidone 40 mg/day for 1 week. Thereafter, the lurasidone dose could be adjusted at regularly scheduled visits within the flexible dose range of 20, 40, 60 or 80 mg/day. In total, 186 (68.6%) patients completed 52 weeks of treatment in the extension study and 156 (57.6%) completed 104 weeks. Averaged across the 104-week open-label treatment period, patients received a mean daily dose of lurasidone of 57.0 mg/day. At extension study baseline, patients had a mean PANSS total score of 76.0 (after a mean change during the initial 6-week double-blind study of −17.5).

Continued improvement (i.e. reduction) in PANSS total score was observed during treatment with open-label lurasidone in the extension study [11]. Mean change in the PANSS total score from baseline in the extension study was −15.6 at week 52 and −18.4 at week 104. Similarly, continued improvement in the CGI-S score was observed during the extension study. Sensitivity analyses that were conducted to investigate the potential impact of early dropouts on the reduction in PANSS total score supported the robustness of the extension study findings.

Progressive improvements in functioning and health-related quality of life (measured using the clinician-rated Children's Global Assessment Scale and the Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire, respectively) were also observed during continued treatment with lurasidone over the extension study [11]. Responder rates (≥20% reduction in PANSS total score from double-blind baseline) and remitter rates (post-hoc analysis; PANSS item scores of ≤3 at one assessment visit on all of eight specified PANSS items [15]) reached ~90% and ~65%,

Table 3 Efficacy of lurasidone in schizophrenia in adolescents in a 6-week phase 3 trial [14]

Study drug	No. of pts	PANSS total score			CGI-S score	
		At baseline (mean)	LSM change from baseline to week 6[a,b]	BGD vs placebo	At baseline (mean)	LSM change from baseline to week 6[b]
Lurasidone 40 mg/day	108	94.5	−18.6**	−8.0	4.9	−1.0**
Lurasidone 80 mg/day	106	94.0	−18.3**	−7.7	4.8	−0.9*
Placebo	112	92.8	−10.5		4.8	−0.5

BGD between-group difference, *CGI-S* Clinical Global Impressions-Severity, *LSM* least-squares mean, *PANSS* Positive and Negative Syndrome Scale, *pts* patients

* $p < 0.01$, ** $p < 0.001$ vs placebo

[a]Primary endpoint

[b]Evaluated using a mixed model for repeated measurement analysis

respectively, after 28 weeks and then plateaued. Responder rates based on more stringent criteria (defined post hoc as a ≥ 50% reduction in PANSS total score from double-blind baseline) were 18.5% at baseline in the extension study and 58.2% and 58.3% at weeks 52 and 104. Further post-hoc analysis found that sustained remission (defined as meeting remission criteria continuously for 6 months) was achieved by 52.8% of patients in the extension study, with a median time to first onset of sustained remission of 64.1 weeks (based on Kaplan-Meier estimation).

What is the tolerability profile of lurasidone in adolescents?

The tolerability profile of lurasidone used in adolescents with schizophrenia is generally consistent with that established for use of the drug in adults with schizophrenia [2, 6, 11, 14]. In the 6-week, double-blind, placebo-controlled trial in adolescents with schizophrenia, adverse events occurring at an incidence of ≥ 5% in either lurasidone dose group and with a numerically higher incidence than in placebo recipients were nausea (incidence 12.7% and 14.4% in lurasidone 40 and 80 mg/day recipients versus 2.7% in placebo recipients), anxiety (10.0% and 2.9% vs 8.0%), somnolence (9.1% and 11.5% vs 5.4%), akathisia (9.1% and 8.7% vs 1.8%), vomiting (8.2% and 6.7% vs 1.8%), sedation (5.5% and 1.9% vs 1.8%), agitation (4.5% and 5.8% vs 4.5%) and EPS-related events excluding akathisia (6.4% and 3.8% vs 1.8%) [14]. Treatment with anticholinergic medications for acute EPS was reported in 4.5%, 2.9% and 1.8% of patients in the respective groups. Numerically fewer patients in the lurasidone 40 and 80 mg/day groups than in the placebo group experienced serious adverse events (3.6% and 1.9% vs 8.0%) and adverse events leading to treatment discontinuation (4.6% and 2.8% vs 8.0%).

No new safety concerns or unexpected adverse events were reported in the open-label extension study with up to 2 years of treatment with lurasidone (with flexible dosing) [11]. In the extension study, serious adverse events were reported in 10.3% of patients (0.115 events per patient-year of exposure) and adverse events leading to discontinuation of lurasidone occurred in 10.7% of patients. As-needed anticholinergic medications were used by 9.6% of patients in the extension study, EPS-related events (excluding akathisia) were reported in 9.6% of patients and akathisia was reported in 8.1% of patients.

Other adverse events of special interest

No clinically meaningful differences in metabolic laboratory parameters, prolactin levels, LSM change in bodyweight or BMI scores were observed between the three treatment groups in the 6-week trial [14]. During longer-term treatment in the extension study, small changes were observed in metabolic parameters, including total cholesterol (median change from baseline in the initial trial to week 104 in the extension trial, −2.0 mg/dL), high-density lipoprotein cholesterol (−3.0 mg/dL), low-density lipoprotein cholesterol (+1.0 mg/dL), triglycerides (+9.0 mg/dL) and insulin (−1.3 mg/dL). Median changes in prolactin levels from double-blind baseline were also minimal during the extension study (females: +1.2 ng/mL at week 52, −0.5 ng/mL at week 104; males: +0.2 ng/mL at week 52, +0.3 ng/mL at week 104) [11]. Mean changes in bodyweight and BMI from double-blind baseline to the end of the 2-year extension study aligned well with those expected in a population of adolescents based on CDC and WHO growth charts, respectively (bodyweight: +4.9 vs +5.7 kg expected; BMI: +0.8 vs +1.0 kg/m^2 expected).

In the 6-week double-blind trial, treatment-emergent suicidal ideation [based on Columbia-Suicide Severity Rating Scale (C-SSRS) measurements] was reported for 5.5% of lurasidone 40 mg/day recipients (including one patient who discontinued the trial because of suicidal ideation), 1.0% of lurasidone 80 mg/day recipients and 4.5% of placebo recipients [14]. In the extension study, 13 patients (4.8%) had emergent or worsening suicidal ideation and three patients (1.1%) had emergent suicidal behaviour based on C-SSRS measurements [11]. Further, suicidal ideation was reported as an adverse event in eight patients, suicidal behaviour in one patient and suicide attempt in one patient. There were no completed suicides, or other deaths, in either the 6-week double-blind trial or the 2-year open-label extension study [11, 14].

What is the current clinical position of lurasidone in schizophrenia in adolescents?

Lurasidone is efficacious and generally well tolerated in the treatment of schizophrenia in adolescents and, having a low propensity for weight gain and other metabolic adverse events commonly associated with second-generation antipsychotics, presents a useful treatment option to consider.

Based on clinical trial data in the acute setting, lurasidone provides clinically meaningful improvements in symptoms of schizophrenia relative to placebo. Furthermore, continued improvement in symptoms is observed during longer-term treatment. The tolerability profile of lurasidone used in adolescents with schizophrenia is generally consistent with the profile established for use in adults. The most commonly observed adverse events during treatment include akathisia and other EPS events, nausea, anxiety, somnolence, vomiting, sedation and agitation, representing a tolerability profile

largely typical for that of a second-generation antipsychotic in schizophrenia patients. However, of note, changes in metabolic parameters and prolactin levels in adolescent lurasidone recipients were minimal over 2 years of treatment, and changes in bodyweight and BMI were consistent with those expected in a population of adolescents. Further, a network meta-analysis that assessed the efficacy and tolerability of lurasidone versus other atypical antipsychotic monotherapies (including aripiprazole, asenapine, clozapine, olanzapine, paliperidone extended-release, quetiapine, risperidone and ziprasidone) found that lurasidone was associated with significantly less weight gain than olanzapine, quetiapine, risperidone, asenapine and paliperidone extended-release [16]. No significant differences between lurasidone and any of the comparators were observed in PANSS or CGI-S score improvement [16].

Guidelines for the treatment of schizophrenia in adolescents recommend use of a second-generation antipsychotic medication in combination with psychological interventions [8, 9]. Head-to-head comparative trials will likely be necessary to accurately position individual antipsychotic agents. Currently, the choice of antipsychotic should be made with consideration of potential adverse events and individual patient factors and preferences.

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