Pharmacokinetics and Tolerability of Lurasidone in Children and Adolescents With Psychiatric Disorders

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ABSTRACT

Purpose: The aim of this study was to evaluate the pharmacokinetic (PK) profile and tolerability of lurasidone in children and adolescents with a range of psychiatric disorders.

Methods: This multicenter, open-label, single and multiple ascending-dose study of the PK profile of lurasidone (20, 40, 80, 120, and 160 mg/d) enrolled outpatients aged 6 to 17 years with a diagnosis of attention deficit/hyperactivity disorder, bipolar spectrum disorder, or other psychiatric disorder. Serial blood samples were collected for analysis of PK parameters, including C_{max}, T_{max}, and $AUC_{0–24}$.

Findings: Exposure (C_{max} and $AUC_{0–24}$) to lurasidone and its active metabolites showed linear increases across the entire dose range. Slope estimates (95% CI) across the dose range studied was 0.90 ng · h/mL (0.74–1.06) for $AUC_{0–24}$ and 0.70 ng/mL (0.52–0.87) for C_{max} on day 10 or 12. Lurasidone exposure, after multiple-dose administration in this child and adolescent population, was similar to exposure observed at steady state in adults. The effects of dose on exposure to the 3 active metabolites of lurasidone were linear and similar after the administration of single and multiple doses. Adverse events were qualitatively similar to those reported in adults. Discontinuations due to adverse events were dose related, with doses $<$120 mg/d being better tolerated than higher doses, especially in younger children.

Implications: In this child and adolescent population, exposure parameters for lurasidone and its active metabolites were dose proportional in the range of 20 to 160 mg/d after the administration of single and multiple doses. These results suggest that lurasidone doses $<$120 mg/d were better tolerated compared with higher doses, especially in younger children. ClinicalTrials.gov identifier: NCT01620060. (*Clin Ther.* 2015;37:2788–2797)

Key words: bipolar I disorder, lurasidone, pediatric, pharmacokinetic, schizophrenia.

INTRODUCTION

Lurasidone is an atypical antipsychotic agent with a distinctive pharmacologic profile characterized by high-affinity binding at serotonin (5-HT)-7 receptors (k_i = 0.5 nM; antagonist) that is comparable to its affinity for dopamine-2 and 5-HT_{2A} receptors. In addition, lurasidone has moderate affinity for 5-HT_{1A} receptors, and minimal to no affinity for H_1 and M_1 receptors.[1] The use of lurasidone was approved by the US Food and Drug Administration in October 2010 for the treatment of adults with schizophrenia, and in July 2013 for the treatment of adults with bipolar depression, both as monotherapy and as adjunctive therapy with lithium or valproate. The efficacy of lurasidone at doses ranging from 20 to 160 mg/d has been investigated in adults with schizophrenia/schizoaffective disorder[2–5] and bipolar disorder.[6,7]

Lurasidone is rapidly absorbed after oral administration, with a mean T_{max} in serum of 1.3 hours.[8] In a study in healthy adult volunteers, 9% to 19% of a given dose was absorbed; absorption was reported to have been linear at doses ranging up to 100 mg/d in healthy volunteers and up to 160 mg/d in individuals with schizophrenia.[8] The mean $t_{½}$ of single-dose lurasidone up to 100 mg/d ranged from 12.2 to 18.3

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hours and increased to 36 hours at steady state (day 9) in healthy volunteers.[8] In adult subjects with schizophrenia administered single doses of 120 to 160 mg/d, the mean $t_{½}$ was 28.8 to 37.4 hours.[8] In a study of multiple-dose lurasidone 120 mg/d in patients with schizophrenia or schizoaffective disorder, steady state was achieved by day 5.[9]

Lurasidone is primarily metabolized by cytochrome P-450 (CYP) 3A4 and is not a substrate of CYP1A1, 1A2, 2A6, 4A11, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1 isozymes. The major biotransformation pathways are oxidative *N*-dealkylation, hydroxylation of norbornane ring, and *S*-oxidation. These pathways produce 2 pharmacologically active metabolites, ID-14283 (the exohydroxy metabolite) and ID-14326, which represent ~25% and 3% of the parent exposure, respectively, and a third minor active metabolite (ID-11614), accounting for 1%.[8] Lurasidone does not induce or inhibit any CYP enzymes. The half-life of the primary active metabolite (ID-14283) is shorter than that of lurasidone, but ID-14283 otherwise has similar pharmacologic and in vivo characteristics.[8]

Data on the PK profile of atypical antipsychotics in child and adolescent patients is important, especially in light of the notable increase in the rate antipsychotic medication use in this population over the past 20 years.[10,11]

The primary objective of the present study was to characterize the PK and tolerability profile of single and multiple oral doses of lurasidone (20, 40, 80, 120, or 160 mg/d) in a child and adolescent population (aged 6–17 years). The secondary objective was to characterize the PK profile of lurasidone metabolites in this population.

PATIENTS AND METHODS

The study protocol was approved by a central institutional review board (Sterling IRB, Atlanta, Georgia), and the study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Patients were enrolled at 8 clinical sites in the United States between June 2012 and May 2013. Before any study procedures were performed, informed consent from the parent or guardian of each child, as well as each patient's assent (or informed consent from emancipated patients), were obtained.

Study Participants

Screening procedures/assessments to determine study eligibility included demographic characteristics and a complete medical history (including complete medication history), vital sign measurements (supine and standing blood pressure, heart rate, and body temperature), height and weight, complete physical examination (including a mental status examination), standard 12-lead ECG (the ECG was read by a central core laboratory, and the read results were used for determining eligibility), clinical laboratory tests (urine drug test and breath alcohol test; hepatitis B and C [only in patients without a documented history]; chemistry [including prolactin], hematology, and urinalysis; and serum pregnancy test [conducted only in female patients aged ≥8 years]).

Eligible subjects were male or female outpatients between the ages of 6 and 17 years (inclusive) with a diagnosis of schizophrenia spectrum disorder, bipolar spectrum disorder, autism spectrum disorder, attention deficit/hyperactivity disorder with aggressive behavior (ie, comorbid conduct disorder or other disruptive behavior disorder), or Tourette's syndrome. Patients were excluded if they had clinically significant alcohol or drug abuse/dependence within the previous 6 months or a positive breath alcohol test or urine screen for drugs of abuse at screening; severe cognitive impairment; clinical instability or an imminent risk for suicide or injury to self, others, or property; a clinically significant major medical condition or abnormal laboratory value or vital sign measurement; and/or pregnancy, breastfeeding, or sexual activity without the use of medically approved birth control. Psychotropic medications were tapered and discontinued at least 3 days before the administration of the first dose of lurasidone, with the exception of fluoxetine (discontinued for ≥28 days) and monoamine oxidase inhibitors (discontinued for ≥14 days). Inhibitors or inducers of CYP3A4 or any medication that could have significantly prolonged the QT/QTc interval was not to be taken within 28 days before study drug administration or at any point during the study and until study termination.

Study Design

In this multicenter, open-label, single and multiple ascending-dose study, patients were stratified into 1 of 4 age groups (6–9, 10–12, 13–15, and 16–17 years) (Figure 1). Dose cohorts were entered into the study sequentially, beginning with the 20-mg/d dose group. Sequentially escalated doses (40, 80, 120, or 160 mg/d) were administered to newly entered patients after PK and tolerability data from the previous dosing cohort