Abstract

**Background:** To evaluate potential drug-drug interactions with the atypical antipsychotic lurasidone.

**Methods:** Seven phase I studies were conducted to investigate the effects of repeated dosing of ketoconazole, diltiazem, rifampin, or lithium on the pharmacokinetics (PK) of single oral doses of lurasidone, or the effects of repeated dosing of lurasidone on the PK of digoxin, midazolam, or the oral contraceptive norgestimate/ethinyl estradiol. Two 6-week, phase III studies included evaluation of the potential for interaction between lurasidone and lithium or valproate. Maximum serum or plasma concentration (C\text{max}) and area under the concentration-time curve (AUC) were calculated.

**Results:** Concomitant ketoconazole administration resulted in a 6.8-fold increase in lurasidone C\text{max} and a 9.3-fold increase in lurasidone AUC; concomitant diltiazem administration resulted in 2.1- and 2.2-fold increases, respectively. Rifampin decreased lurasidone C\text{max} and AUC (one-seventh and one-fifth of lurasidone alone, respectively). Steady-state dosing with lurasidone increased C\text{max} and AUC\text{0–24} (AUC from time 0 to 24 h postdose) of digoxin by 9% and 13%, respectively, and of midazolam by 21% and 44%, respectively. There were no significant interactions between lurasidone and lithium, valproate, ethinyl estradiol, or norelgestromin (the major active metabolite of norgestimate).

**Conclusions:** Lurasidone PK is altered by strong cytochrome P450 (CYP) 3A4 inhibitors or inducers, and coadministration is contraindicated; whereas moderate CYP3A4 inhibitors have less effect, and lurasidone dosage restrictions are recommended. No dose adjustment for lurasidone is needed when administered with lithium or valproate. Dose adjustment is not required for lithium, valproate, digoxin (a P-glycoprotein substrate), or midazolam or oral contraceptives (CYP3A4 substrates) when coadministered with lurasidone.

**Keywords:** atypical antipsychotic; drug interactions; lurasidone; pharmacokinetics.

Introduction

Lurasidone HCl, an oral atypical antipsychotic agent approved in the US, Canada, and Switzerland for the treatment of schizophrenia (dose range 40–160 mg/day) and in the US for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression, dose range 20–120 mg/day), is a benzisothiazol derivative that acts as an antagonist with high affinity for dopamine D\text{2}, serotonin 5-HT\text{2A}, and 5-HT\text{7} receptors. Lurasidone also has moderate antagonist activity at α\text{2A} and α\text{2C} adrenergic receptors and partial agonist activity at 5-HT\text{1A} receptors, but has little affinity for histamine H\text{1} receptors or M\text{1} muscarinic receptors [1].

Lurasidone is metabolized predominantly by hepatic cytochrome P450 (CYP) 3A4 isoenzyme 3A4, yielding two non-major, active metabolites (ID-14283 and ID-14326), two major, nonactive metabolites (ID-20219 and ID-20220), and a nonmajor, nonactive metabolite (ID-11614) [2, 3]. Thus, there is potential for drug-drug interactions between lurasidone and drugs that are metabolized by CYP3A4 or are CYP3A4 inducers or inhibitors. The energy-dependent efflux transporter P-glycoprotein (P-gp) is also involved in absorption, distribution, metabolism, and excretion of drugs [4]. In LLC-PK1 cells expressing human P-gp, lurasidone demonstrated an inhibitory effect on digoxin transport activity at a concentration of 1–10 μM [half...
maximal inhibitory concentration (IC\textsubscript{50})=1 \mu\text{M} \) (unpublished data). Based on \textit{in vitro} studies, lurasidone is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 enzymes [5]. Because lurasidone is not a substrate for CYP1A2, smoking is not expected to have an effect on lurasidone pharmacokinetics (PK).

Medical comorbidities are highly prevalent in people with severe mental disorders, including schizophrenia and bipolar disorder [6]. Thus, it is common for patients with schizophrenia or bipolar disorder to receive concomitant medications, some of which are CYP3A4 inhibitors or inducers or are substrates or inhibitors of P-gp, for other medical and psychiatric disorders. Moreover, lurasidone may be used by women of childbearing age who are taking an oral contraceptive. Therefore, a series of seven phase I studies were undertaken between June 2004 and January 2009 to investigate potential drug-drug interactions between lurasidone and drugs that are known substrates, inhibitors, or inducers of CYP3A4 or P-gp, or are commonly coadministered to patients with schizophrenia. In addition, two phase III registration studies, conducted from May 2009 through August 2012, included evaluation of the potential interaction between adjunctive lurasidone (20–120 mg/day) and lithium or valproate.

For Studies 1–3, the primary objective was to evaluate the effects of multiple oral dosing with the interacting drug (ketoconazole, a strong CYP3A4 inhibitor, Study 1; diltiazem, a moderate CYP3A4 inhibitor, Study 2; rifampin, a strong CYP3A4 inducer, Study 3) on the PK parameters of single oral doses of lurasidone (10–40 mg). For Study 4, the primary objective was to evaluate the effect of multiple oral dosing with lithium, a drug commonly coadministered with antipsychotic agents, on the steady-state PK of lurasidone. Two phase III studies (Study 5 and Study 6) were conducted to evaluate the efficacy and safety of adjunctive lurasidone (20–120 mg/day) for the treatment of bipolar depression; assessment of serum drug concentrations permitted evaluation of potential drug-drug interactions of lurasidone with lithium or valproate during 6 weeks of coadministration. For phase I Studies 7 and 8, the primary objective was to evaluate the effect of lurasidone on other drugs (digoxin, a P-gp substrate, Study 7; midazolam, a CYP3A4 substrate, Study 8) by comparing the steady-state PK of the test drug administered alone or after steady-state dosing with lurasidone 120 mg/day. For Study 9, the primary objective was to evaluate the effect of lurasidone 40 mg on the PK of ethinyl estradiol and norelgestromin, the major active metabolite of norgestimate [7, 8], after concomitant administration of a combination oral contraceptive product containing ethinyl estradiol 0.035 mg and norgestimate 0.180, 0.215, or 0.250 mg (Ortho Tri-Cyclen	extsuperscript{*}; Ortho-McNeil-Janssen Pharmaceuticals, Inc., Raritan, NJ, USA) [9]. The secondary objective in all of the phase I studies was to evaluate the safety of concomitant administration of lurasidone and the interacting drugs.

### Materials and methods

All studies were approved by Institutional Review Boards at each study center and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to enrollment. Details of the study designs are summarized in Table 1. In all studies, lurasidone was taken with a meal.

### Pharmacokinetic analyses

In the phase I studies, serum concentrations of lurasidone and interacting drugs were measured utilizing validated liquid chromatography-tandem mass spectrometry methods. The lower limit of quantification was 0.02 ng/mL for lurasidone, 0.05 ng/mL for digoxin, 0.1 ng/mL for midazolam and 1-hydroxymidazolam, and 5 pg/mL for ethinyl estradiol and norelgestromin. Precision (expressed as percent coefficient of variation (% CV) or relative standard deviation (RSD)) varied by study, ranging from 1.7% to 10.8%; accuracy ranged from 89.9% to 109.1%. PK parameters were estimated using WinNonlin\textsuperscript{*} version 5.3 (Pharsight, Cary, NC, USA) via noncompartmental methods. Maximum serum or plasma concentrations (C\textsubscript{max}) of lurasidone and interacting drugs were obtained directly from concentration-time profiles. Estimates of the area under the concentration-time curve (AUC) varied by study and included AUC from time 0 to 24 h (AUC\textsubscript{0–24}), AUC from time 0 to the last quantifiable drug concentration (AUC\textsubscript{0–\text{last}}), and AUC from time 0 extrapolated to infinity (AUC\textsubscript{0–\infty}), and AUC from time 0 to dosing interval at steady state (AUC\textsubscript{\infty}). All AUCs were calculated using the linear-log trapezoidal rule.

In the phase III studies of adjunctive lurasidone treatment for bipolar depression (Studies 5 and 6) [10, 11], patients were required to have serum levels in the therapeutic range for lithium (0.6 to 1.2 mEq/L) or valproate (50–125 μg/mL). PK parameters were obtained for lithium and for valproate at baseline and after 6 weeks of coadministration with lurasidone; lurasidone PK was assessed in Study 5 but not Study 6.

### Safety assessments

In all studies, safety was assessed by monitoring adverse events, physical examination, measurements of vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations. Adverse events were defined as any untoward medical occurrences in subjects receiving study medication; all such events were assessed for severity and relationship to study medication.
<table>
<thead>
<tr>
<th>Study number</th>
<th>Interacting drug</th>
<th>Study design and site(s)</th>
<th>Study population</th>
<th>Lurasidone dose and timing&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Interacting drug dose and timing&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Timing of pharmacokinetic assessments</th>
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<td><strong>Phase I studies of the effects of coadministered drug on lurasidone PK</strong></td>
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<tr>
<td>Study 1</td>
<td>Ketoconazole</td>
<td>Open-label, single-sequence crossover, Phase I, single site, US</td>
<td>Healthy male volunteers age 18–45 years</td>
<td>Day 1: single oral dose of lurasidone 10 mg&lt;br&gt;Day 11: lurasidone 10 mg</td>
<td>Days 7–10: ketoconazole 400 mg once daily&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;Day 11: ketoconazole 400 mg&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;Days 12 and 13: ketoconazole 400 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Days 1 and 11: blood samples collected predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 28, 36, 48, and 72 h postdose</td>
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<td>Study 2</td>
<td>Diltiazem</td>
<td>Randomized, placebo-controlled, fixed-sequence, two-period fixed-sequence, Phase I, single site, US</td>
<td>Healthy male and female volunteers age 18–45 years</td>
<td>First treatment period: single oral dose of lurasidone 20 mg or placebo&lt;br&gt;Second treatment period (day 5): single dose of lurasidone or placebo</td>
<td>Second period: open-label diltiazem 240 mg once daily for 7 days&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Days 1 and 5: blood samples collected predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 28, 36, 48, and 72 h postdose</td>
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<tr>
<td>Study 3</td>
<td>Rifampin</td>
<td>Open-label, two treatment periods, Phase I, single site, US</td>
<td>Healthy male and female volunteers age 18–45 years</td>
<td>First treatment period: single oral dose of lurasidone 40 mg&lt;br&gt;Second treatment period (day 8): single oral dose of lurasidone 40 mg</td>
<td>Second period: oral rifampin 600 mg once daily for 8 days&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Day 1, period 1&lt;br&gt;Day 8, period 2&lt;br&gt;Blood samples collected predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 h postdose</td>
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<td>Study 4</td>
<td>Lithium</td>
<td>Open-label, two 8-day treatment periods, Phase I, single site, US</td>
<td>Male and female subjects with clinically stable schizophrenia, schizoaffective disorder, or schizophréniform disorder according to DSM-IV-TR, age 18–65 years</td>
<td>Both treatment periods: lurasidone 120 mg once daily for 8 days</td>
<td>Second treatment period: lithium carbonate 600 mg twice daily for 8 days&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;Morning dose: lithium given concurrently with lurasidone&lt;sup&gt;e&lt;/sup&gt;&lt;br&gt;Evening dose: lithium given ~12 h later&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Day 8 of each treatment period&lt;br&gt;Blood samples collected predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h postdose</td>
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<td><strong>Phase III studies of lurasidone as adjunctive treatment for bipolar depression</strong></td>
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<td>Study 5</td>
<td>Lithium or valproate</td>
<td>Double-blind, placebo controlled, parallel group, Phase III, 58 sites, 23 in the US</td>
<td>Male and female subjects with bipolar I disorder, most recent episode depressed, with or without rapid cycling disease course and without psychotic features, diagnosed according to DSM-IV-TR criteria, age 18–75 years</td>
<td>Days 1–3: lurasidone 20 mg once daily&lt;br&gt;Days 4–6: lurasidone 40 mg once daily&lt;br&gt;Day 7: lurasidone 60 mg once daily&lt;br&gt;Day 8–week 6: flexible dosing, lurasidone 20–120 mg once daily</td>
<td>Lithium was dosed (300–2400 mg/day) to ensure that trough serum levels were in the range of 0.6 to 1.2 mEq/L&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;Valproate was dosed (300–2000 mg/day) to ensure that trough serum levels were in the range of 50 to 125 μg/mL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Screening, baseline, and weeks 1, 4, and 6 for lithium and valproate; weeks 3, 4, and 6 for lurasidone</td>
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<tr>
<td>Study number</td>
<td>Interacting drug</td>
<td>Study design and site(s)</td>
<td>Study population</td>
<td>Lurasidone dose and timing</td>
<td>Interacting drug dose and timing</td>
<td>Timing of pharmacokinetic assessments</td>
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<td>Study 6</td>
<td>Lithium or valproate</td>
<td>Double-blind, placebo controlled, parallel-group Phase III, 71 sites, 22 in the US</td>
<td>Male and female subjects with bipolar I disorder, most recent episode depressed, with or without rapid cycling disease course and without psychotic features, diagnosed according to <em>DSM-IV-TR</em> criteria, age 18–75 years</td>
<td>Days 1–3: lurasidone 20 mg once daily Days 4–6: lurasidone 40 mg once daily Day 7–week 6: flexible dosing, lurasidone 20–120 mg once daily</td>
<td>Lithium was dosed (300–1500 mg/day) to ensure that trough serum levels were in the range of 0.6 to 1.2 mEq/L Valproate was dosed (300–2000 mg/day) to ensure that trough serum levels were in the range of 50 to 125 μg/mL</td>
<td>Screening, baseline, and weeks 3 and 6 for lithium and valproate</td>
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<td>Study 7</td>
<td>Digoxin</td>
<td>Open-label, sequential Phase I, single site, US</td>
<td>Male and female subjects with schizophrenia, schizoaffective disorder, or schizophreniform disorder, diagnosed according to <em>DSM-IV-TR</em> criteria, age 18–65 years</td>
<td>Days 6–12: lurasidone 120 mg once daily Days 13 and 14: lurasidone 120 mg</td>
<td>Day 1: Single oral dose of digoxin 0.25 mg* Days 13 and 14: digoxin 0.25 mg*</td>
<td>Days 1 and 13: blood samples collected predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, and 48 h postdose</td>
</tr>
<tr>
<td>Study 8</td>
<td>Midazolam</td>
<td>Open-label, sequential Phase I, single site, US</td>
<td>Male and female subjects with schizophrenia, schizoaffective disorder, or schizophreniform disorder, diagnosed according to <em>DSM-IV-TR</em> criteria, age 18–65 years</td>
<td>Days 6–14: lurasidone 120 mg once daily</td>
<td>Day 1: single oral dose of midazolam 5 mg (2.5 mL of a 2.0 mg/mL syrup)* Days 6 and 13: midazolam 5 mg*</td>
<td>Days 1, 6, and 13: blood samples collected predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h postdose</td>
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<tr>
<td>Study 9</td>
<td>Ortho Tri-Cyclen</td>
<td>Double-blind, placebo-controlled, two-way crossover with a 28-day lead-in period, followed by two consecutive 28-day treatment periods, during which volunteers received 1 tablet daily Phase I, single site, US</td>
<td>Healthy female volunteers, age 18–40 years</td>
<td>First treatment period: lurasidone 40 mg or placebo once daily on days 12–21 Second treatment period: switched to the other treatment on days 12–21</td>
<td>Each day: subjects were asked to take their oral contraceptive tablet at specified times and to record the exact time of dosing</td>
<td>Day 21 of each treatment period: blood samples collected predose and 0.33 (20 min), 0.67 (40 min), 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 48 h postdose</td>
</tr>
</tbody>
</table>

*DSM-IV-TR*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* [12]. aAdministered with 240 mL of water, 30 min after receiving a standard breakfast (ketoconazole, diltiazem, Ortho Tri-Cyclen studies) or a standard high-fat breakfast (rifampin, lithium, digoxin, and midazolam studies) or in the evening with (or within 30 min of) a meal (phase III studies). bRifampin was administered approximately 1 h before breakfast following a fast of ≥8 h because food is known to decrease the bioavailability of rifampin [13]. cTo minimize side effects, the lithium dose was titrated to the target of 0.6 to 1.2 mEq/L (mmol/L). The lithium daily dose was modified in a 300-mg increment if the serum concentration was below 0.6 mEq/L and titrated down in a 300-mg decrement if the serum concentration was above 1.2 mEq/L. dThe evening dose of lithium was administered approximately 12 h following the morning dose, given with 240 mL water and a light snack.
Statistical analyses

In each study, descriptive statistics were used to describe lurasidone serum concentrations and PK parameters. In the ketoconazole study (Study 1), changes in lurasidone $C_{\text{max}}$, $\text{AUC}_{0\text{-last}}$, and $\text{AUC}_{0\text{-inf}}$ in the presence and absence of ketoconazole were calculated for each subject. Point estimates with 90% confidence intervals (CIs) for the ratios of these PK parameters in the presence and absence of ketoconazole were calculated by subtraction of log-transformed values. Only descriptive statistics were used in this study.

For Studies 2 (diltiazem), 3 (rifampin), and 4 (lithium), mixed-effects analyses of variance (ANOVA) were applied to log-transformed lurasidone PK parameters ($C_{\text{max}}$ and $\text{AUC}$). Geometric means and 90% CIs were calculated for each PK parameter and for the ratios of each PK parameter in the presence and absence of the interacting drug. Significant interactions with lurasidone were determined to have occurred if the 90% CIs for the ratios of geometric mean PK parameters were outside the range of 80.0% to 125.0%.

To evaluate the effect of lithium or valproate on lurasidone PK in a phase III study (Study 5), a previously developed population PK model served as the reference group. This model was developed on the basis of data from 1913 subjects (healthy volunteers and patients with schizophrenia, schizoaffective disorder, or bipolar disorder) in the lurasidone clinical trial database who received single-dose or multiple-dose lurasidone (20–600 mg/day), without lithium or valproate, for up to 6 weeks. Lurasidone serum concentration data were obtained after 6 weeks of coadministration of lithium ($n=84$) or valproate ($n=80$) in Study 5. These data were added to the lurasidone serum concentration data set, and an additional parameter was estimated to allow a shift in apparent clearance ($CL/F$) for subjects who received lurasidone+lithium or lurasidone+valproate in Study 5. On the basis of the small shift in $CL/F$, the population estimate for lurasidone $\text{AUC}_{0\text{-last}}$ with or without lithium or valproate, was calculated.

For the evaluation of the effect of lurasidone on the PK of lithium or valproate, data were pooled from two phase III studies in patients with bipolar depression (Studies 5 and 6), mean (SD) trough serum concentration ($C_{\text{trough}}$) was obtained for lithium or valproate in the presence and absence of lurasidone, and geometric mean ratios were calculated.

In the phase I studies evaluating the effect of lurasidone on the PK of other drugs (Studies 7, 8, and 9), $C_{\text{max}}$ and $\text{AUC}$ were log-transformed and analyzed by mixed-effects ANOVA. In Studies 7 (digoxin) and 8 (midazolam), treatment was modeled as a fixed effect, and subject was modeled as a random effect. Geometric means were calculated for each PK parameter on each study day, and the ratio of geometric means in the presence and absence of lurasidone, together with the corresponding 90% CIs, were calculated. In Study 8 (midazolam), this statistical analysis was applied to the parent drug but not the active metabolite 1-hydroxymidazolam, for which PK parameters were summarized descriptively.

In Study 9 (Ortho Tri-Cyclen), separate models appropriate for a placebo-controlled, two-period crossover study were used; the models included treatment, period, and treatment sequence as fixed effects, and subject within treatment sequence as a random effect. Two-sided CIs for the treatment differences in $C_{\text{max}}$ and $\text{AUC}_{0\text{-last}}$ in the presence and absence of lurasidone were derived from these models and used to calculate the 90% CIs for the ratio of geometric mean parameters in the presence and absence of lurasidone. The effect of lurasidone on the PK of ethinyl estradiol and norelgestromin would be judged nonsubstantial if all 90% CIs were contained in the range of 80.0% to 125.0%.

Results

Baseline demographic and clinical characteristics of all subjects are summarized in Table 2. In general, subjects with schizophrenia or bipolar disorder tended to be older and to have a higher body mass index (BMI) compared with healthy volunteers.

Effect of coadministered drugs on the PK of lurasidone

PK parameters ($C_{\text{max}}$ and $\text{AUC}$) and 90% CIs are summarized in Table 3 and presented graphically in Figure 1A.

Study 1 (phase I, ketoconazole)

Mean serum concentrations at all time points up to 72 h after dosing were higher for lurasidone coadministered with ketoconazole than with lurasidone alone. In the presence of ketoconazole, lurasidone $C_{\text{max}}$ increased 6.8-fold and $\text{AUC}_{0\text{-last}}$ increased 9.3-fold (Table 3), findings consistent with inhibition of CYP3A4 by ketoconazole.

Study 2 (phase I, diltiazem)

Concentrations at all time points up to 72 h after dosing were higher in the presence of diltiazem than when lurasidone was administered alone. The 90% CIs for the ratios of geometric mean $C_{\text{max}}$ and $\text{AUC}$ were outside the range of 80.0% to 125.0% (Table 3), indicating a significant interaction between lurasidone and diltiazem.

Study 3 (phase I, rifampin)

In the presence of rifampin, lurasidone $C_{\text{max}}$, $\text{AUC}_{0\text{-last}}$, and $\text{AUC}_{0\text{-inf}}$ were decreased by approximately 82% to 85%. The 90% CIs for the ratios of geometric mean PK parameters were outside the range of 80.0% to 125.0% (Table 3), indicating a significant interaction between lurasidone and rifampin.

Study 4 (phase I, lithium)

Lurasidone serum concentrations in the presence and absence of lithium were similar at all time points. The point estimates of the ratio of geometric means indicate
Table 2  Baseline demographic and clinical characteristics of subjects in each study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phase I studies, effects of coadministered drug on lurasidone PK</th>
<th>Phase III studies</th>
<th>Phase I studies, effects of lurasidone on coadministered drug PK</th>
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<td>Study 1</td>
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<td><strong>Interacting drug(s)</strong></td>
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<td>Diltiazem</td>
<td>Rifampin</td>
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<tr>
<td><strong>Subjects</strong></td>
<td>Healthy volunteers</td>
<td>Healthy volunteers</td>
<td>Healthy volunteers</td>
</tr>
<tr>
<td><strong>Subjects enrolled/completed, n</strong></td>
<td>10/9</td>
<td>14/12</td>
<td>20/20</td>
</tr>
<tr>
<td><strong>Sex, n (male/female)</strong></td>
<td>10/0</td>
<td>7/7</td>
<td>20/0</td>
</tr>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>28.6 (8.6)</td>
<td>26.6 (6.9)</td>
<td>27.6 (5.5)</td>
</tr>
<tr>
<td><strong>Weight, kg, mean (SD)</strong></td>
<td>72 (7.3)</td>
<td>78.0 (13.9)</td>
<td>83.8 (12.8)</td>
</tr>
<tr>
<td><strong>BMI, kg/m², mean (SD)</strong></td>
<td>22.9 (1.7)</td>
<td>25.8 (3.8)</td>
<td>25.8 (2.9)</td>
</tr>
</tbody>
</table>

SD, standard deviation. *Patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder diagnosed by DSM-IV-TR criteria [12]. **Patients with bipolar I disorder, most recent episode depressed, diagnosed by DSM-IV-TR criteria. *Patients randomized to receive lurasidone+lithium or valproate. **Patients randomized to receive placebo+lithium or valproate.

that $C_{\text{max}}$ decreased by 8% and $AUC_{0-\tau}$ increased by 7% in the presence of lithium. The 90% CI for the lurasidone $AUC_{0-\tau}$ ratio in the presence and absence of lithium was within the 80.0% to 125.0% range. The corresponding $C_{\text{max}}$ ratio was slightly outside of this range, which was not considered clinically meaningful (75.5% to 112.2%; Table 3).

**Study 5 (phase III, lithium or valproate)**

The population estimated $AUC_{0-24}$ of lurasidone was similar in subjects who received lurasidone plus lithium or lurasidone plus valproate compared with those who received lurasidone alone; the 90% CIs for the $AUC_{0-24}$ ratio were within the 80.0% to 125.0% range, indicating the absence of a clinically meaningful interaction (Table 3).

**Effect of lurasidone on the PK of coadministered drugs**

PK parameters ($C_{\text{max}}$, $C_{\text{trough}}$, and AUC) and 90% CIs are summarized in Table 4 and presented graphically in Figure 1B.

**Pooled Studies 5 and 6 (phase III, lithium or valproate)**

Geometric mean $C_{\text{trough}}$ was similar for the interacting drug (lithium or valproate) alone (baseline) and in the presence of lurasidone (week 6); the 90% CIs for the $C_{\text{trough}}$ ratio were within the 80.0% to 125.0% range, indicating the absence of a clinically meaningful interaction (Table 4). Subjects’ exposure to the interacting drug was similar at baseline (lithium mean dose of 897–933 mg, median of 900 mg; valproate mean dose of 1058–1068 mg, median of 1000 mg) and week 6 (lithium mean dose of 904–949 mg, median of 900 mg; valproate mean dose of 1054–1056 mg, median of 1000 mg).

**Study 7 (phase I, digoxin)**

Comparison of the digoxin geometric mean parameters in the presence and absence of lurasidone showed that $C_{\text{max}}$ increased by 9% and $AUC_{0-24}$ by 13% in the presence of lurasidone. The 90% CIs for the ratios of the geometric mean PK parameters in the presence and absence of lurasidone were within the 80.0% to 125.0% range for $AUC_{0-24}$ but not for $C_{\text{max}}$ (range, 93.1% to 128.5%; Table 4).
Table 3: Mean (SD) C_{max}, AUC, and geometric mean ratio (90% CI) for lurasidone in the presence and absence of ketoconazole, diltiazem, rifampin, and lithium (phase I Studies 1–4), and lithium or valproate (phase III Study 5).

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Study 1 ketoconazole (n=10)</th>
<th>Study 2 diltiazem (n=10)</th>
<th>Study 3 rifampin (n=20)</th>
<th>Study 4 lithium (n=20)</th>
<th>Phase III study (Study 5)</th>
<th>Lithium (n=84)</th>
<th>Valproate (n=80)</th>
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<tr>
<td>C_{max}, ng/mL</td>
<td></td>
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<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lurasidone alone</td>
<td>6.5 (3.0)</td>
<td>23.3 (6.8)</td>
<td>33.4 (11.1)</td>
<td>118.0 (43.8)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lurasidone plus interacting drug</td>
<td>44.0 (9.2)^b</td>
<td>49.4 (14.5)</td>
<td>4.94 (1.7)</td>
<td>124.0 (85.9)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Geometric mean ratio (90% CI)</td>
<td>6.92 (5.76–8.30)</td>
<td>2.10 (1.77–2.47)</td>
<td>0.15 (0.12–0.18)</td>
<td>0.92 (0.76–1.12)</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>AUC, ng·h/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lurasidone alone</td>
<td>21.7 (9.7)^d</td>
<td>108.6 (25.5)^e</td>
<td>153.0 (47.2)^e</td>
<td>647 (289)^f</td>
<td>401 (385–418)^g</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lurasidone plus interacting drug</td>
<td>201.8 (30.2)^h</td>
<td>233.1 (44.4)^e</td>
<td>28.0 (9.6)^e</td>
<td>749 (391)^f</td>
<td>438 (386–501)^g</td>
<td>379 (334–441)^g</td>
<td>–</td>
</tr>
<tr>
<td>Geometric mean ratio (90% CI)</td>
<td>8.95 (7.54–10.62)</td>
<td>2.16 (1.92–2.44)</td>
<td>0.19 (0.17–0.22)</td>
<td>1.07 (0.96–1.20)</td>
<td>1.09 (0.97–1.04)</td>
<td>0.95 (0.84–1.09)</td>
<td>–</td>
</tr>
</tbody>
</table>

AUC, area under the serum concentration-time curve; CI, confidence interval; C_{max}, maximum serum concentration; SD, standard deviation. ^bImpact of lithium or valproate on lurasidone PK was estimated using population PK modeling methodology. ^d=n=9. ^fLurasidone plus interacting drug/lurasidone alone. ^gAUC_{0–last}, ^hAUC_{0–inf}, ^iAUC_{0–24}, ^jAUC_{0–τ} (90% CI).

Study 8 (phase I, midazolam)

Concentrations of midazolam increased slightly following coadministration of lurasidone, whereas 1-hydroxy-midazolam concentrations did not change following either single or multiple doses of lurasidone. The ratio of geometric mean C_{max} for midazolam alone and after steady-state dosing with lurasidone on Day 13 was 121.5%, and the corresponding value for AUC_{0–24} was 137.9%. In both cases, the 90% CI for these ratios overlapped the upper bound of the 80.0% to 125.0% range (Table 4), suggesting a weak inhibitory effect of lurasidone on CYP3A4.

Study 9 (phase I, Ortho Tri-Cyclen)

Concentrations of ethinyl estradiol and norelgestromin following administration of Ortho Tri-Cyclen were similar when the oral contraceptive was taken alone or with lurasidone. For each contraceptive steroid, geometric mean C_{max} and AUC_{0–24} were similar in both periods, and the 90% CI for the ratio of geometric mean parameters in the presence and absence of lurasidone was contained within the 80.0% to 125.0% range (Table 4), indicating no significant interaction between lurasidone and either contraceptive steroid. In a separate study, sex hormone-binding globulin concentrations were not meaningfully affected when Ortho Tri-Cyclen was coadministered with lurasidone (unpublished data).

Adverse events

The most common adverse events that occurred during administration of lurasidone in the phase I studies were somnolence (85/134; 63.4%), akathisia (33/134; 24.6%), and dystonia (23/134; 17.2%). The vast majority of adverse events in the phase I studies were rated by the investigator as mild or moderate. Severe adverse events experienced by patients receiving lurasidone were dystonia [1 subject in Study 4 (lithium), while receiving lurasidone alone], somnolence [1 subject in Study 8 (midazolam), while receiving midazolam alone, and again while receiving midazolam and lurasidone], and dysmenorrhea [1 subject in Study 9 (Ortho Tri-Cyclen) while receiving Ortho Tri-Cyclen and lurasidone].

Serious adverse events in the phase I studies included a moderate elevation in creatine phosphokinase experienced by one patient during administration of lurasidone and lithium, leading to hospitalization; this adverse event resolved after the end of the study. In Study 7 (digoxin), one serious adverse event (moderate worsening of psychotic symptoms) was reported, with onset 16 days after the last dose of study medication.
Interacting drug

Ketoconazole 400 mg/day
Diltiazem 240 mg/day
Rifampin 600 mg/day
Lithium 600 mg BID
Lithium 300–2400 mg/day
Valproate 300–2000 mg/day

PK Fold change and 90% CI

Change relative to lurasidone alone

Interacting drug

Digoxin 0.25 mg, single dose
Midazolam 5 mg, single dose
Ethinyl estradiol
Norelgestromin
Lithium 300–2400 mg/day
Valproate 300–2000 mg/day

PK Fold change and 90% CI

Change relative to interacting drug alone

Figure 1 Effects of coadministered drugs on the PK of lurasidone (A) and the effects of steady-state dosing with lurasidone on the PK of coadministered drugs (B).

A

B

*Steady-state C_{trough} on week 6 vs. baseline when coadministered with lurasidone at steady state. AUC, area under the concentration-time curve; BID, twice daily; CI, confidence interval; C_{max}, maximum serum or plasma concentration; C_{trough}, trough serum or plasma concentration; PK, pharmacokinetic(s); SD, single dose.

In the two phase III studies of bipolar depression, the most common adverse events with lurasidone were nausea (14%), extrapyramidal symptoms (EPS; 14%), somnolence (11%), and akathisia (11%) [5]; additional information on the safety and tolerability of lurasidone in the treatment of bipolar depression is available elsewhere [5, 10]. Because concomitant treatment with lithium and an antipsychotic agent may increase the risk for EPS [14], the incidence of EPS-related adverse events was evaluated in greater detail in these two studies of adjunctive lurasidone in bipolar depression (Table 5). With the exception of parkinsonism and tremor, which were somewhat more common in patients who received lurasidone and lithium compared to those who received lithium and placebo, the incidence of individual EPS was generally low. No incidences of EPS were severe, and there were no study discontinuations resulting from EPS. Rates of akathisia were higher in subjects receiving lithium and adjunctive lurasidone (14.0%) compared with lithium alone (9.0%) and in subjects receiving...

(digoxin+lurasidone). In Study 9 (Ortho Tri-Cyclen), two serious adverse events related to a traffic accident that resulted in hospitalization occurred in a single subject receiving Ortho Tri-Cyclen alone. Three other subjects (all in the phase I lithium study) discontinued study participation because of adverse events (one subject receiving lurasidone who had nausea and emesis and two subjects receiving lurasidone and lithium: the subject described above with elevated creatine phosphokinase and another with akathisia, dystonia, and tremor).

In the two phase III studies of bipolar depression, the most common adverse events with lurasidone were...
Table 4  Mean (SD) $C_{\text{trough}}$ for lithium and valproate (phase III Studies 5–6) and mean (SD) $C_{\text{max}}$ and AUC for digoxin, midazolam, and the oral contraceptives ethinyl estradiol and norelgestromin (phase I Studies 7–9) following administration alone and during steady-state dosing with lurasidone, with geometric mean ratios and 90% CIs.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Pooled Studies 5 and 6</th>
<th>Study 7 digoxin (n=23)</th>
<th>Study 8 Midazolam (n=24)</th>
<th>Study 9 oral contraceptivea (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lithium (n=115)</td>
<td>Valproate (n=172)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}/C_{\text{trough}}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interacting drug alone</td>
<td>0.67 (1.55)b</td>
<td>62.5 (1.90)b</td>
<td>0.7 (0.3)</td>
<td>11.4 (4.4)</td>
</tr>
<tr>
<td>Lurasidone plus interacting drug</td>
<td>0.66 (1.67)d</td>
<td>58.3 (2.23)d</td>
<td>0.7 (0.2)</td>
<td>13.4 (3.8)e</td>
</tr>
<tr>
<td>Geometric mean ratio (90% CI)f</td>
<td>0.98 (0.90–1.08)</td>
<td>0.93 (0.83–1.05)</td>
<td>1.09 (0.93–1.29)</td>
<td>1.21 (1.09–1.36)e</td>
</tr>
<tr>
<td>$\text{AUC}_{0-24}$, ng·h/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interacting drug alone</td>
<td>–</td>
<td>–</td>
<td>4.6 (1.2)</td>
<td>62.7 (17.0)</td>
</tr>
<tr>
<td>Lurasidone plus interacting drug</td>
<td>–</td>
<td>–</td>
<td>5.1 (1.1)</td>
<td>85.4 (21.8)e</td>
</tr>
<tr>
<td>Geometric mean ratio (90% CI)f</td>
<td>–</td>
<td>–</td>
<td>1.13 (1.04–1.23)</td>
<td>1.38 (1.26–1.51)e</td>
</tr>
</tbody>
</table>

AUC, area under the serum concentration-time curve; CI, confidence interval; $C_{\text{max}}$, maximum serum concentration; $C_{\text{trough}}$, trough serum concentration; SD, standard deviation. aOrtho Tri-Cyclen (ethinyl estradiol 0.035 mg and norgestimate 0.180 mg, 0.215 mg, or 0.250 mg). bInteracting drug at study baseline. cpg/mL. dLurasidone plus interacting drug at week 6. e$n=23$. fLurasidone plus interacting drug/interacting drug alone. gpg·h/mL.

Table 5  Incidence of adverse events related to akathisia and EPS that occurred in at least one subject in any treatment group of the phase III clinical trials of adjunctive lurasidone for bipolar depression.

<table>
<thead>
<tr>
<th>Adverse event, n (%)a</th>
<th>Pooled Studies 5 and 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lithium+placebo (n=134)</td>
</tr>
<tr>
<td>Akathisia</td>
<td>12 (9.0)</td>
</tr>
<tr>
<td>Cogwheel rigidity</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Drooling</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Glabellar reflex abnormal</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Muscle rigidity</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tremor</td>
<td>9 (6.7)</td>
</tr>
<tr>
<td>Trismus</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

aThere were no cases of bradykinesia, extrapyramidal disorder, hypokinesia, oculogyric crisis, oromandibular dystonia, tongue spasm, or torticollis.

valproate and lurasidone (8.6%) compared with valproate alone (2.0%). Severe akathisia was noted in three patients receiving lithium and lurasidone and one patient receiving valproate and lurasidone but did not lead to study discontinuation.

Discussion

CYP3A4 is the principal hepatic enzyme responsible for drug metabolism. It has been estimated that this enzyme metabolizes 50% of marketed drugs [15], including many...
psychotropic medications such as antidepressants and antipsychotic agents [16, 17]. Circulating plasma/serum concentrations of such drugs may be influenced by coadministration of drugs that inhibit or induce CYP3A4 [18]. In Study 1, serum concentration of lurasidone was increased in the presence of ketoconazole, an effect consistent with inhibition of CYP3A4 by ketoconazole. Conversely, in Study 3, rifampin reduced $C_{\text{max}}$ and AUC$_{0\text{--}t}$ of lurasidone by more than 80% due to induction of CYP3A4.

Ketoconazole and rifampin are known potent inhibitors and inducers, respectively, of CYP3A4; hence, drug interactions would be expected when these agents are coadministered with a drug that is predominantly metabolized by CYP3A4, such as lurasidone. Thus, strong inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, and mibefradil) or inducers (e.g., rifampin, St. John’s wort, phenytoin, and carbamazepine) of CYP3A4 should not be coadministered with lurasidone and should be discontinued prior to initiating lurasidone therapy [5]. If a strong inducer of CYP3A4 is discontinued in a patient already taking lurasidone, the dose of lurasidone may need to be reduced to preserve tolerability and safety; conversely, the dose of lurasidone may need to be increased in order to maintain efficacy if a strong inhibitor of CYP3A4 is discontinued.

Similar interactions with ketoconazole and rifampin have been reported for other antipsychotic agents that are wholly or partly metabolized by CYP3A4. Inhibition of CYP3A4 by ketoconazole has been shown to result in increased plasma concentrations or decreased clearance of several atypical antipsychotics, including clozapine, quetiapine, ziprasidone, and risperidone [19–21]. Studies in healthy volunteers have shown that rifampin decreases plasma concentrations and increases clearance of risperidone [22, 23], and there is evidence implicating rifampin in a clinically significant interaction with clozapine [24]. Such interactions may also be anticipated with quetiapine [20].

Although drug interactions involving strong inhibitors or inducers of CYP3A4 have been well characterized, it is necessary to examine potential interactions with commonly used drugs that have only moderate inhibitory effects on CYP3A4. For this reason, Study 2 investigated potential interactions between lurasidone and an anti-hypertensive drug, diltiazem, a calcium channel blocker. The changes in the PK of lurasidone 20 mg/day observed in this study (two-fold increases in $C_{\text{max}}$ and AUC when lurasidone was coadministered with diltiazem) indicated that the dose of lurasidone should be reduced with coadministration of diltiazem. It is recommended that the dose of lurasidone not exceed 80 mg/day in combination with a moderate CYP3A4 inhibitor such as diltiazem [5].

Studies 7, 8, and 9 investigated the effects of lurasidone on the PK of digoxin, midazolam, and the oral contraceptive steroids ethinyl estradiol and norelgestromin, respectively. Digoxin is a substrate for P-gp [25–27] and is potentially susceptible to interactions involving drugs that inhibit or induce this transporter. CYP3A4 inhibitors or inducers often have corresponding effects on P-gp [25]. Although preclinical data suggest that lurasidone inhibits P-gp (unpublished data), administration of lurasidone 120 mg/day to subjects with schizophrenia had no significant effect on plasma digoxin $C_{\text{max}}$ and produced only a slight increase in digoxin AUC$_{0\text{--}24}$.

Midazolam is a substrate for CYP3A4 and is a sensitive probe for changes in the activity of this enzyme [28]. Steady-state dosing with lurasidone resulted in 21% and 44% increases in midazolam $C_{\text{max}}$ and AUC$_{0\text{--}t}$, respectively; these changes are not regarded as clinically meaningful. Additionally, concentrations of 1-hydroxymidazolam, a metabolite of midazolam, were not affected by lurasidone.

Given the widespread use of oral contraceptives among women of childbearing potential [29], it may be anticipated that a considerable number of patients for whom lurasidone is prescribed will be taking concomitant contraceptive steroids. Clinically relevant interactions with oral contraceptives have been reported with a number of medications, including antiepileptic drugs, rifampin, and broad-spectrum antibiotics [29, 30]. In many cases, such interactions are attributable to induction of CYP isoenzymes involved in the metabolism of ethinyl estradiol [29]. In Study 7, no significant changes in the PK of ethinyl estradiol or norelgestromin were observed following steady-state dosing with lurasidone 40 mg/day.

Study 4 investigated the effect of lithium on the PK of lurasidone because lithium, although not hepatically metabolized, is often coadministered with antipsychotic drugs [31]. Drug interactions resulting in increased plasma lithium concentrations have been reported with a number of commonly used drugs that affect water or electrolyte balance, including some nonsteroidal anti-inflammatory drugs, thiazide diuretics, and angiotensin-converting enzyme inhibitors [32]. Conversely, lithium has been reported to increase concentrations of certain drugs, such as amisulpride, an atypical antipsychotic agent [33]. In Study 4, lithium (600 mg twice daily) had little effect on serum lurasidone $C_{\text{max}}$ or AUC$_{0\text{--}t}$ following multiple dosing with lurasidone (120 mg/day).

In the analysis of pooled data from two 6-week, phase III studies of adjunctive lurasidone in bipolar depression (Studies 5 and 6), neither lithium nor valproate mean $C_{\text{rough}}$ was significantly altered following 6 weeks of administration of lurasidone (flexibly dosed from 20 to 120 mg/day).
The analysis of lurasidone PK data using population PK modeling methodology showed that neither lithium (flexibly dosed from 300 to 2400 mg/day) nor valproate (flexibly dosed from 300 to 2000 mg/day) had a significant effect on serum lurasidone AUC0–τ, which is consistent with the findings of the phase I lithium study (Study 4).

Concomitant use of lithium and an antipsychotic agent may increase the risk for EPS [14]. This analysis of EPS-related adverse event data from two phase III studies of adjunctive lurasidone in patients with bipolar depression found that the incidence of individual EPS was generally low. Akathisia, parkinsonism, and tremor were somewhat more common during concomitant treatment with lithium and lurasidone than with valproate and lurasidone. There were no adverse events indicative of central nervous system neurotoxicity in subjects who received lurasidone in combination with lithium.

In conclusion, relatively few drug-drug interactions were observed with lurasidone, with the notable exception of those that occurred in the presence of strong CYP3A4 inhibition or induction. Drugs that are strong CYP3A4 inhibitors or inducers should not be coadministered with lurasidone, and the lurasidone dose should not exceed 80 mg/day when coadministered with a moderate CYP3A4 inhibitor. No dose adjustment for lurasidone is needed when coadministered with lithium or valproate. Furthermore, dose adjustment is not required for lithium, valproate, digoxin (a P-gp substrate), or midazolam or oral contraceptives (CYP3A4 substrates) when coadministered with lurasidone.

ClinicalTrials.gov identifiers: NCT00868452 (StudyD1050235), NCT01284517 (Study D1050292), NCT01082276 (Study D1050270, rifampin), NCT01074073 (Study D1050247, lithium), NCT01082289 (Study D1050279, digoxin), NCT01082263 (Study D1050269, midazolam), NCT00549666 (Study D1050246, oral contraceptive). Study D1050183 (ketoconazole) and Study D1050250 (diltiazem) were completed prior to the requirement to register trials.

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References