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A non-randomized study to investigate the effects of the atypical antipsychotic aripiprazole on the steady-state pharmacokinetics of lamotrigine in patients with bipolar I disorder†

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Objective To determine the effect of aripiprazole on steady-state pharmacokinetics of lamotrigine in patients with bipolar I disorder who were clinically stable on lamotrigine (100–400 mg/day) for ≥4 weeks.
Methods In this open-label study, aripiprazole was administered at 10 mg/day for 3 days, 20 mg/day for 3 days, then 30 mg/day for 8 days. Blood samples were collected on Days –1 and 14 for determination of lamotrigine steady-state pharmacokinetic parameters. Safety and tolerability were assessed.
Results Eighteen patients were administered aripiprazole in combination with lamotrigine. Geometric mean (GM) values for lamotrigine maximum plasma concentration were similar for lamotrigine alone (26 ng/mL) and with co-administered aripiprazole (23 ng/mL). GM values for plasma lamotrigine area under the concentration–time curve (AUC_τ) were comparable for lamotrigine alone (434 ng/h/mL) and with co-administered aripiprazole (394 ng/h/mL). Median T_{max} of lamotrigine alone and combined with aripiprazole was 1.98 and 0.77 h, respectively. No changes to lamotrigine dose-normalized plasma trough concentrations were observed with co-administered aripiprazole. Sixteen patients (88.9%) experienced ≥1 adverse event (AE), the most common of which was insomnia ($n = 6$).
Conclusions Aripiprazole had no meaningful effect on lamotrigine steady-state pharmacokinetics in patients with bipolar I disorder. No dosage adjustment of lamotrigine is required and the combination was generally safe and well tolerated. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — atypical antipsychotic; aripiprazole; lamotrigine; pharmacokinetics; bipolar I disorder

INTRODUCTION

Bipolar disorder is a chronic mood disorder that has a high rate of recurrence and frequently requires combination therapy for effective symptom control. Antipsychotics are widely used in the initial treatment of mania either as monotherapy or in combination with mood stabilizers, lithium or anticonvulsants (Bowden, 2004; Keck *et al*., 2000). Atypical antipsychotics are preferred to conventional antipsychotics because they have equivalent efficacy and a more favorable safety profile with a lower risk of neurological side effects (APA, 2002; Goodwin, 2003; Tohen *et al*., 2001). However, many atypical antipsychotics are associated with unwanted adverse events (AEs), including weight gain, metabolic syndrome, hyperlipidemia and hyperglycemia (Allison and Casey, 2001), hyperprolactinemia (Turrone *et al*., 2002), and QTc prolongation (Glassman and Bigger, 2001).

Aripiprazole is an atypical antipsychotic that has been approved by the US Food and Drug Administration for the acute and maintenance treatment of manic and mixed episodes associated with bipolar I disorder at doses of up to 30 mg once daily. This atypical antipsychotic has a pharmacologically distinct profile of dopamine D_2/D_3 and serotonin $5HT_{1A}$ partial agonism and serotonin $5HT_{2A}$ antagonism (Jordan *et al*., 2002, 2004; Shapiro *et al*., 2003) and has been shown to be effective and safe in the treatment of patients with bipolar I disorder (Dillenschneider et al., 2007; Keck et al., 2003, 2006, 2007; Sachs et al., 2006; Vieta et al., 2005, 2007; Zimbroff et al., 2007).

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Aripiprazole is metabolized extensively, primarily through cytochrome P-450 CYP3A4 and CYP2D6 (DeLeon *et al*., 2004; Swainston Harrison and Perry, 2004). These enzymes catalyze the conversion of aripiprazole to dehydro-aripiprazole, the major active metabolite of aripiprazole that has similar potency to the parent compound. Dehydro-aripiprazole is also a substrate for CYP3A4. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are more than 99% bound to serum proteins, predominantly to albumin (Swainston Harrison and Perry, 2004).

Aripiprazole has linear pharmacokinetics when administered once daily at doses up to 90 mg/day, and steady state is typically reached within 14 days. The mean half-life values of aripiprazole and dehydro-aripiprazole are 75 and 100 h, respectively (Mallikaarjun *et al*., 2004; Saha *et al*., 2002).

In bipolar I disorder, lamotrigine has demonstrated efficacy and safety for maintenance monotherapy (Bowden *et al*., 2003; Calabrese *et al*., 2003). Lamotrigine is metabolized predominantly by glucuronic acid conjugation, mainly by UDP-glucuronosyltransferase 1A4 (UGT1A4) (Green *et al*., 1995) with the inactive 2-N-glucuronide conjugate as the major metabolite. Following single oral doses, the half-life values of lamotrigine ranged from 14 to 68 h (Elwes and Binnie, 1996), whereas multiple dosing of lamotrigine in healthy subjects autoinduces its metabolism, resulting in a 25% decrease in half-life values and a 37% increase in apparent oral clearance at steady state compared with values obtained in the same person following a single dose (Lamictal, 2007). Administration of lamotrigine has been associated with the onset of Stevens–Johnson syndrome, a severe and life-threatening cutaneous reaction (Rzany *et al*., 1999; Schlienger *et al*., 1998). Therefore, safety is an important outcome to assess when adding a medication to lamotrigine therapy.

Lamotrigine and aripiprazole are both approved for the maintenance treatment of bipolar I disorder in the USA and it is possible that the medications may be prescribed in combination. Hence, there is a requirement to establish whether any drug–drug interactions will occur between these two agents.

AIM

The aim of this study was to assess the steady-state pharmacokinetics of lamotrigine during co-administration with aripiprazole in patients with bipolar I disorder.

METHODS

Study design

This 14-day, open-label, non-randomized study was approved by the Heartland, Copernicus, RCRC and Aspire Institutional Review Boards, and the Albert Einstein Healthcare Network, and conducted in accordance with the ethical principles of the Declaration of Helsinki at six sites. All patients provided written informed consent prior to study entry. The study enrolled patients 18–65 years of age with bipolar I disorder (DSM-IV-TR (APA, 2000)) who were clinically stable, as determined by the treating physician or investigator based on relevant medical records. Patients were required to have been on an established regimen of lamotrigine ($\geq$100 mg/day) that might also have included lithium and/or gabapentin for at least 4 weeks prior to screening. If applicable, patients were required to have trough serum plasma lithium levels that were less than the recommended therapeutic maximum concentration ($\leq$1.4 mM at screening). Lithium and gabapentin were not expected to alter the pharmacokinetics of either aripiprazole or lamotrigine.

Exclusion criteria included: nursing or pregnant women; any significant acute or chronic medical illness; diagnosis of epilepsy or dementia; presence of psychotic symptoms; history of recent (within 6 months) drug or alcohol abuse; patients receiving carbamazepine or medications classified as cytochrome P450 3A4 inducers or inhibitors; evidence of organ dysfunction; any clinically significant deviation from normal in the physical, vital signs, electrocardiographic or clinical laboratory examinations; positive blood screen for hepatitis C antibody.

Study treatments

To ensure steady-state conditions for lamotrigine pharmacokinetics, no lamotrigine dose adjustments were permitted for 4 weeks before or during the study. A maximum of three psychotropic agents were allowed, including lithium and/or gabapentin, provided that the patient was on a stable dose for at least 4 weeks before screening. Use of other mood stabilizers and concomitant medications was limited.

The study design is outlined in Figure 1. In order to minimize tolerability issues after aripiprazole administration, doses of aripiprazole were increased gradually from 10 mg/day to a target of 30 mg/day, which is the maximum recommended daily dose. On Days 1–3, patients were administered aripiprazole at a once-daily dose of 10 mg/day. On Day 4, the dose was increased to

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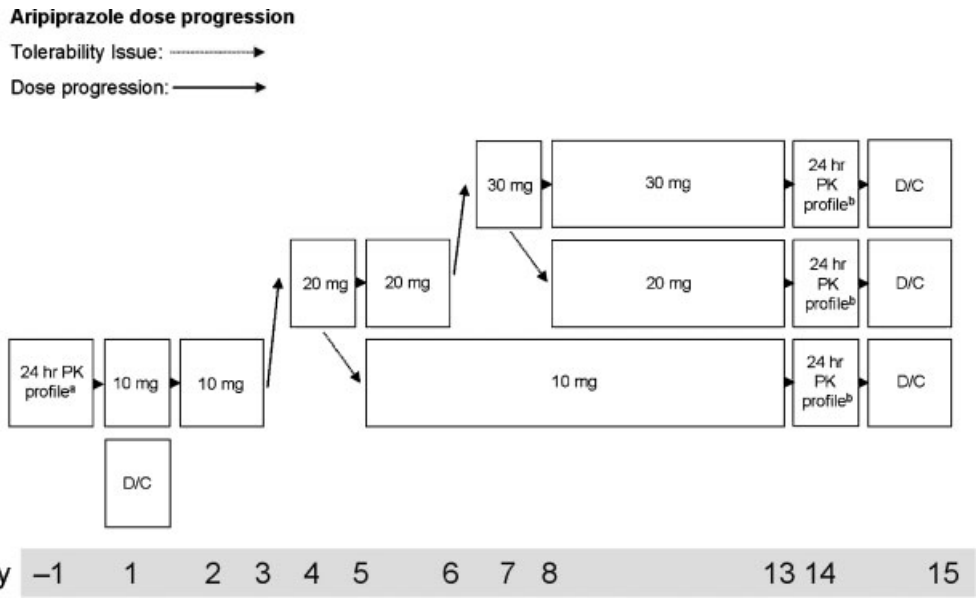

Figure 1. Schematic of study design. Doses are daily doses of aripiprazole: [a]24-h PK profile of lamotrigine, [b]24-h PK profile of lamotrigine and C_{min} values for aripiprazole and dehydroaripiprazole followed by study discharge on Day 15. D/C = discharged from study; PK = pharmacokinetic

20 mg/day for 3 days; on Day 7, the dose was increased to 30 mg/day for the remaining 8 days. If a patient was unable to tolerate aripiprazole at 20 or 30 mg/day, the dose could be reduced to the maximum tolerated dose ($\geq$10 mg/day). Patients unable to tolerate aripiprazole at 10 mg/day were discontinued from the study. Patients remained in the clinical facility from Day –5 until discharge from the study on Day 15.

Patients were not permitted to consume alcohol or products containing grapefruit from 4 days before introduction of aripiprazole until the end of the study. On days when blood samples were taken for pharmacokinetic analysis, patients had to fast (with only water permitted) for 10 h prior to, and 4 h after, the aripiprazole dosing.

Pharmacokinetic assessments

Serial blood samples were collected on Days 1 and 14 to characterize the pharmacokinetics of lamotrigine. On these days, venous blood was collected at each of the following timepoints relative to lamotrigine administration: 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 h. On Days 14 and 15, predose blood samples were taken for the trough plasma concentrations (C_{min}) of aripiprazole and dehydro-aripiprazole for the assessment of steady-state. All blood samples were collected in ethylenediaminetetraacetic acid (EDTA)-containing tubes. Immediately after collection, tubes were gently inverted and then stored at 4°C until they were centrifuged for 10 min at $1000 \times g$ (4°C). Sample processing was completed within 70 min of collection and serum samples were stored at ≤ -20°C.

Plasma samples were analyzed for lamotrigine, aripiprazole and dehydro-aripiprazole concentrations by validated LC-MS/MS assays within the known period of analyte stability.

For analysis of lamotrigine plasma concentrations, analytes were extracted from 200 μL of plasma by liquid–liquid extraction using ter-butyl ether. After evaporation and reconstitution, extracts were assayed for lamotrigine by positive electrospray single mass spectrometry. The standard curve range was 50.2–10032 ng/mL, representing the lower and upper limits of quantification, respectively. Values for the between-run precision and the within-run precision for lamotrigine analytical quality control samples were no greater than 6.2% coefficient of variation (CV), with deviations from the nominal concentrations of no more than ±3.4%.

For analysis of aripiprazole and dehydro-aripiprazole plasma concentrations, analytes were extracted from 200 μL of plasma by protein precipitation using acetonitrile. Following evaporation, samples were reconstituted and extracts were assayed by liquid chromatography with atmospheric pressure ionization tandem mass spectrometry detection. The standard curve range for aripiprazole and dehydro-aripiprazole was 1.0–250 ng/mL, representing the lower and upper limits of quantification, respectively. Values for the between-run and the within-run precision for aripiprazole and dehydro-aripiprazole analytical quality

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control samples were no greater than 7.1% CV, with deviations from the nominal concentrations of no more than ±7.0%.

Pharmacokinetic parameters for lamotrigine were derived from plasma concentration versus time data. The following pharmacokinetic parameters were determined: maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration–time curve over the dosing interval (area under the concentration–time curve, AUC_τ) and C_{min}. To determine the effect of aripiprazole on the steady-state pharmacokinetics of lamotrigine, the log-transformed C_{max} and AUC_τ were analyzed by analysis of variance (ANOVA), in the presence and absence of aripiprazole, and point estimates and 90% confidence intervals (CIs) for ratios of geometric means (GMs) of C_{max} and AUC_τ were calculated. Lack of an effect of aripiprazole on lamotrigine steady-state pharmacokinetics can be concluded if the 90% CIs for the ratio of population GMs of aripiprazole plus lamotrigine to lamotrigine alone are contained within 80–125% for both C_{max} and AUC_τ of lamotrigine.

Safety and tolerability assessments

AEs were recorded throughout the study by spontaneous reporting or open-ended questioning. Information on severity, likely relationship to study drug and outcome were reported. Vital sign measurements, electrocardiograms, physical examinations, and clinical laboratory tests were also performed at screening, baseline (Day 1) and at study discharge (Day 15).

Statistical analysis

If the 90% CIs for aripiprazole plus lamotrigine to lamotrigine alone ratios of GMs were contained within 80–125% for both C_{max} and AUC_τ of lamotrigine, it was concluded that there was a lack of effect of aripiprazole on lamotrigine steady-state pharmacokinetics. If the true ratio of population GMs is 1, it was calculated that data from 12 patients provided at least 90% power with respect to both C_{max} and AUC_τ of lamotrigine to conclude that aripiprazole has no effect on the pharmacokinetics of lamotrigine.

To determine the effect of aripiprazole on the steady-state pharmacokinetics of lamotrigine, point estimates, and 90% CIs were constructed for aripiprazole plus lamotrigine to lamotrigine alone ratios of GMs for C_{max} and AUC_τ of lamotrigine, based on appropriate analyses of variance.

Summary statistics were tabulated for lamotrigine T_{max} and for lamotrigine C_{max} and AUC_τ (normalized by lamotrigine dose) by treatment (lamotrigine alone, aripiprazole plus lamotrigine).

RESULTS

Patients

A total of 35 patients were screened for inclusion in this study, and 18 received treatment with adjunctive aripiprazole. The demographics of the patients are shown in Table 1. The mean age of patients was 39 years (27–55 years) and most study participants were male and Caucasian. Of the 18 patients who received treatment, two discontinued (Day 2, $n = 1$; Day 8, $n = 1$). The reasons for study discontinuation were withdrawal of consent by one patient; the second patient had a positive urine ethanol test and no longer met study criteria. At the end of the study (Day 14), 15 participants were receiving aripiprazole at 30 mg/day (one patient withdrew consent after 1 day of dosage). One patient received aripiprazole at 10 mg/day throughout the study. At the end of the study, the distribution of patients receiving lamotrigine was as follows: 100 mg/day, $n = 13$; 150 mg/day, $n = 1$; 200 mg/day, $n = 1$; 400 mg/day, $n = 1$. Of the mood stabilizers permitted in this study, one patient entered the study on lithium and continued on lithium at a dose of 900 mg/day (serum lithium concentration of 0.5 mEq/L). None of the patients entered the study on gabapentin or received gabapentin during the study.

Pharmacokinetics

The dose-normalized pharmacokinetic parameters for lamotrigine alone, and in combination with aripipra-

Table 1. Patient demographics

	Total, $n = 18$
Age (years)	
Mean (SD)	39 (9)
Gender, n (%)	
Male	12 (67)
Female	6 (33)
Race, n (%)	
White	11 (61)
Black/African American	7 (39)
Weight (kg)	
Mean (SD)	86.7 (15.8)
Height (cm)	
Mean (SD)	174.2 (9.0)
Body Mass Index (kg/m^2)	
Mean (SD)	28.6 (4.8)

SD, standard deviation.

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Table 2. Dose-normalized pharmacokinetic parameters for lamotrigine alone and with aripiprazole

	Lamotrigine pharmacokinetic parameters		
	Lamotrigine only ($n = 16$)	Lamotrigine + aripiprazole ($n = 16$)	Ratio lamotrigine: aripiprazole/lamotrigine (90% CI)
C_{max} (ng/mL)/mg			
Geometric mean	26	23	0.898 (0.829, 0.972)
CV (%)	38	32	
AUC_τ (ng•h/mL)/dose			
Geometric mean	434	394	0.909 (0.849, 0.973)
CV (%)	44	40	
Median t_{max} (h)			
(range)	1.98 (0.5–24.0)	0.77 (0.0–6.0)	n/a
C_{min} (ng/mL/mg)			
Geometric mean	15	13	n/a
CV (%)	57	57	

AUC_τ, area under the concentration–time curve; C_{max}, maximum plasma concentration; C_{min}, plasma trough concentration; CI, confidence interval; CV, coefficient of variation; n/a, not applicable; t_{max}, time to reach C_{max}; h, hours.

zole, are shown in Table 2. The combination of lamotrigine with aripiprazole had no major effects on the steady-state pharmacokinetics of lamotrigine (Figure 2 and Table 2). The 90% CIs for the GM ratios of dose-normalized lamotrigine C_{max} and AUC_τ with and without aripiprazole were contained entirely within 80–125%. Thus, the predefined criteria to conclude a lack of interaction between the two drugs was met.

The dose-normalized GM (CV%) C_{max} values for lamotrigine were similar for lamotrigine alone (26 [38] [ng/mL]/mg) and in combination with aripiprazole (23 [32] [ng/mL]/mg). Similarly, the GM (CV%) for lamotrigine AUC_τ were comparable for lamotrigine alone versus a combination of lamotrigine and aripiprazole (434 [44] [ng•h/mL]/mg vs. 394 [40] [ng•h/mL]/mg, respectively) (Table 2). The dose-normalized plasma concentration versus time curves for lamotrigine alone and in combination with aripiprazole were similar (Figure 2), although a decrease in median T_{max} values was observed when lamotrigine and aripiprazole were co-administered (lamotrigine: 1.98 h; lamotrigine + aripiprazole: 0.77 h). There appeared to be no difference to the dose-normalized lamotrigine C_{min} either predose or post-dose between Days 1 and 14 of the study (Table 3). Furthermore, the C_{min} values of aripiprazole co-administered with lamotrigine were similar to those observed with lamotrigine alone, irrespective of whether samples were collected predose or post-dose and at the beginning or end of the study.

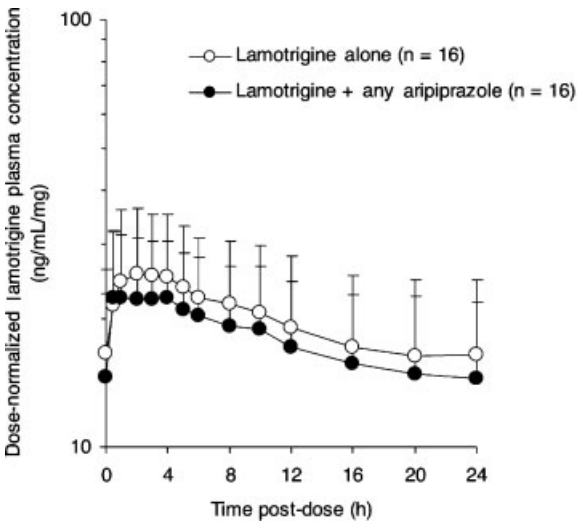

Figure 2. Mean (±SD) plasma concentration versus time profiles of lamotrigine at steady state following administration alone and with aripiprazole

The mean [correction made here after initial online publication] C_{min} values for aripiprazole measured on day 14 at 0 h (261.06 ng/mL) and 24 h (251.92 ng/mL), and for dehydro-aripiprazole on Day 14 at 0 h (74.83 ng/mL) and 24 h (77.32 ng/mL), indicate that both analytes appeared to be at steady state.

Safety and tolerability

Of the 18 patients who received aripiprazole in this study, 16 patients (88.9%) experienced one or more AEs. A total of 61 AEs occurred in 17 (94.4%) patients who received any study drug. All but two of the reported AEs were mild-to-moderate in intensity. One patient reported two severe AEs: dyspepsia lasting 30 min (unlikely to be treatment-related) and dystonia lasting 30 min (considered probably treatment-related). AEs occurring with an incidence of >10% are listed in Table 4. The most common AEs were insomnia ($n = 6$; 33.3%), headaches ($n = 4$; 22.2%), and restlessness

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Table 3. Summary statistics for lamotrigine trough plasma concentrations by day and treatment

		Trough plasma concentrations			
Treatment		Day –1, 0 h (ng/mL/mg)	Day –1, 24 h (ng/mL/mg)	Day 14, 0 h (ng/mL/mg)	Day 14, 24 h (ng/mL)
Lamotrigine alone	N	16	16	16	16
	GM	1482	1493	1281	1327
	CV (%)	57	50	57	51
10 mg aripiprazole + lamotrigine	N	1	1	1	1
	Conc.	948	877	892	820
30 mg aripiprazole + lamotrigine	N	15	15	15	15
	GM	1527	1547	1313	1370
	CV (%)	56	48	57	50

CV, coefficient of variation; GM, geometric mean; Conc., concentration; h, hours.

($n = 4$; 22.2%). No serious AEs or deaths were reported. There were no events of Stevens–Johnson syndrome in any of the 16 patients who completed the study. Twelve patients had ECG abnormalities before study treatment, with 11 participants exhibiting abnormalities at study discharge. The majority of these abnormalities were non-specific ST/T abnormalities, voltage criteria for left ventricular hypertrophy and early repolarization; these were present at either screening, prestudy on Day –1 and/or study discharge. These abnormalities were not considered by the investigator to be clinically relevant.

No marked laboratory abnormalities or clinically relevant changes between the orthostatic vital signs at baseline or at the end of the study were observed.

DISCUSSION

This open-label, non-randomized study assessed the effect of aripiprazole (10, 20, or 30 mg/day) on the steady-state pharmacokinetics of lamotrigine in patients with bipolar I disorder. There were no clinically significant drug–drug interactions, and aripiprazole, dosed to or near steady-state, did not alter the steady-state pharmacokinetics of lamotrigine (100–400 mg/day). The combination of these agents was safe and well tolerated.

Table 4. Adverse events that occur with an incidence of >10%

	n (%)
Total number of AEs	61
Total patients with AEs	17 (94.4)
Insomnia	6 (33.3)
Restlessness	4 (22.2)
Headache	4 (22.2)
Anxiety	3 (16.7)
Logorrhoea	3 (11.1)
Nausea	3 (16.7)
Akathisia	2 (11.1)
Psychomotor hyperactivity	2 (11.1)
Dyspepsia	2 (11.1)
Toothache	2 (11.1)
Dystonia	2 (11.1)
Agitation	2 (11.1)
Irritability	2 (11.1)
Somnolence	2 (11.1)
Back pain	2 (11.1)

AE, adverse event.

The design of the study maximized the possibility of observing drug–drug interactions of aripiprazole with clinically relevant lamotrigine doses. Successful titration of aripiprazole from 10 to 30 mg/day over 2 weeks was achieved, with 15 of the 16 patients who completed the study achieving the maximum recommended dose (30 mg/day). The similarity of the mean trough plasma concentrations of aripiprazole and dehydro-aripiprazole showed that steady-state or near steady-state conditions had been achieved; these values were comparable to those observed previously in patients with schizophrenia who had received aripiprazole at 30 mg/day (Citrome *et al*., 2005), suggesting that there were no drug–drug interactions between aripiprazole and lamotrigine.

The point estimates (90% CI) for GM ratios of dose-normalized lamotrigine C_{max} and AUC_{τ}, both with and without aripiprazole, were 0.989 (0.829, 0.972) and 0.909 (0.849, 0.973), respectively. The 90% CIs were entirely contained within 80–125%, meeting the prespecified criteria to conclude that there was a lack of interaction between lamotrigine and aripiprazole at steady state. Although the upper bounds of the 90% CIs for lamotrigine C_{max} and AUC_{τ} GMs were less than 1.0, suggesting a consistent reduction in lamotrigine exposure of ~10%, it is unlikely that this will be of clinical consequence.

The lack of effect of aripiprazole on the steady-state pharmacokinetics of lamotrigine was anticipated, given their different routes of metabolism. Aripiprazole is predominantly metabolized by CYP2D6 and CYP3A4 and does not undergo direct glucuronidation, whereas lamotrigine is metabolized by glucuronic acid conjugation. There is no evidence to suggest that lamotrigine inhibits the metabolism of drugs elimi-

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nated via CYP2D6 and CYP3A4. Indeed, no alterations to systemic lamotrigine concentrations have previously been observed with other atypical antipsychotics that are metabolized by cytochrome P450 enzymes (Reimers *et al*., 2005). In one study undertaken in a routine clinical setting, co-administration of lamotrigine with either clozapine, which is primarily metabolized by CYP1A2, or risperidone, which is cleared via CYP2D6 and CYP4A3 enzymes, was seen to have no significant effect on dose-normalized lamotrigine serum levels (Reimers *et al*., 2005). Similarly, no clinically significant interactions were observed when lamotrigine was co-administered with olanzapine (Jann *et al*., 2006). Furthermore, aripiprazole does not affect the disposition of co-administered drugs that are primarily metabolized through glucuronidation (e.g., lorazepam). Concomitant administration of lorazepam and aripiprazole injection in healthy subjects resulted in no significant changes to the pharmacokinetic parameters of either drug (Abilify, 2007), and it has been observed that co-administration of aripiprazole and valproate resulted in no clinically significant effects on the pharmacokinetics of aripiprazole (Citrome *et al*., 2005) or alterations to valproate pharmacokinetic parameters (Boulton *et al*., 2004).

In agreement with these studies, the data in this paper demonstrate that the combination of aripiprazole with agents that are metabolized by glucuronic acid results in no adverse drug–drug interactions, and this appears to be an acceptable treatment regimen.

The combination of aripiprazole with lamotrigine was generally safe and well tolerated. No serious AEs were observed and most reported AEs were mild-to-moderate in intensity. Moreover, although Stevens–Johnson syndrome has previously been observed after administration of lamotrigine alone (Schlienger *et al*., 1998; Rzany *et al*., 1999) and in combination with valproate (Yalcin and Karaduman, 2000), the addition of aripiprazole to a stable dose of lamotrigine did not induce onset of this syndrome, although with the caveat of the small sample size in this study.

In conclusion, co-administration of aripiprazole with lamotrigine had no effect on the pharmacokinetics of lamotrigine in patients with bipolar I disorder. No meaningful changes were observed in the C_{max} and AUC_{τ} of lamotrigine when administered in combination with aripiprazole. Thus, a pharmacokinetic drug–drug interaction for lamotrigine is not expected to occur. The co-administration of lamotrigine and aripiprazole was generally safe and well tolerated. Based on the absence of change within the pharmacokinetic parameters, it appears that no dose adjustment for lamotrigine is needed when co-administered with aripiprazole.

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