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The Effect of Food on the Absorption of Oral Ziprasidone

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ABSTRACT *~ Oral ziprasidone bioavailability is increased when taken with food. Here we describe two pharmacokinetic studies to quantify the impact of food on ziprasidone absorption in healthy volunteers. The first, an open-label, six-way crossover study, investigated ziprasidone absorption in eight healthy men. Subjects received oral ziprasidone (20, 40, and 80 mg) after an 8-hour fast or immediately following a US Food and Drug Administration standard meal (50% fat). In this study, area under the serum concentration-time curve (AUC) was greater in fed than in fasting states at each dose (20 mg, +48%; 40 mg, +87%; 80 mg, +101%). Under fasting conditions, increases in AUC and maximum drug concentration (C_{max}) were less than dose-proportional; under fed conditions, they were dose-proportional. The second, an open-label, randomized, three-way crossover study, explored the impact of dietary fat on ziprasidone absorption in 14 healthy subjects. Subjects received ziprasidone (40 mg) under three conditions: fasting, with a high-fat meal (60% fat), and with a moderate-fat (30% fat) meal. AUC and C_{max} under fed conditions increased by 104% and 84% (60%-fat meal) and 79% and 98% (30%-fat meal) , respectively, relative to the fasting state. There was no clear difference in ziprasidone bioavailability between the fed groups, suggesting that meal fat content is not a major determinant of bioavailability. Less pharmacokinetic variability was observed in the fed state, suggesting more consistent absorption of ziprasidone. These results demonstrate that administration of ziprasidone with food is crucial to ensure optimal, reliable dose-dependent bioavailability and thus predictable symptom control and tolerability.* Psychopharmacology Bulletin. *2007;40(3):58-68.*

INTRODUCTION

Food, particularly the fat content of meals, influences the absorption of many orally administered drugs.[1] For many lipophilic drugs, absorption is enhanced when taken with food.

Ziprasidone (5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2-*H*-indol-2-one) is a widely used atypical antipsychotic indicated for the treatment of schizophrenia[2] and bipolar disorder.[3] It is a highly lipophilic compound, and this property impacts its absorption profile with respect to food.

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The prescribing information for ziprasidone specifies that the capsules should be taken with food.[4]

Previous pharmacokinetic studies have shown that under fasting conditions, oral doses of ziprasidone (0.5–40 mg) resulted in approximately dose-proportional increases in mean maximum observed serum concentration (C_{max}) and mean area under the serum concentration-time curve from time 0–12 hours $(AUC)_{0–12}$. Under these fasting conditions, this dose proportionality was lost at higher doses, although there was evidence of some increase in overall exposure. When the dose of ziprasidone was taken after food, dose proportionality was seen in the dose range between 20 and 60 mg.[5] A further study showed that the administration of a single 20-mg dose of ziprasidone in the fed state produced total AUC ($AUC_{0–\infty}$) and C_{max} values 69% and 67% greater, respectively, than values in the fasting state, and that taking ziprasidone 2 hours after a meal reduced drug absorption compared with taking it with food.[6]

The aims of the pharmacokinetic studies described here were to extend previous investigations of the effect of food and, specifically, to quantify the impact of the fat content of food on ziprasidone absorption, and to evaluate the pharmacokinetic linearity and dynamics of drug absorption in relation to fed and fasting conditions at drug doses above 40 mg.

METHODS

Study 1

Study Design. An open-label, nonrandomized, six-way crossover study was conducted in eight healthy male volunteers. Single oral doses of ziprasidone were administered in ascending order, first under fasting conditions and then under fed (nonfasting conditions), i.e., 20 mg fasting, 20 mg fed, 40 mg fasting, 40 mg fed, 80 mg fasting, and 80 mg fed. Ziprasidone capsules (20 mg) were used for all doses (1 × 20 mg, 2 × 20 mg, and 4 × 20 mg). Each subject who completed the study received all six doses, with at least 7 days separating each treatment day. Other than on study days, subjects were allowed to maintain their usual diet throughout the study.

Subjects were confined to the research facility under continuous medical or paramedical supervision for at least 12 hours prior to, and until at least 24 hours after, each dose. On the night before each dosing day, subjects fasted for 8 hours prior to dosing, or to consuming a standard, high-fat breakfast consisting of two eggs, bacon, ham, toast with butter and jelly, and 8 oz of whole milk as suggested by the US Food and Drug Administration (FDA).[7] Caffeinated beverages were not allowed. After breakfast (consumed over no more than 20 minute), ziprasidone was

administered immediately with 50 mL of water. On the mornings when ziprasidone was to be administered in the fasting state, the capsule(s) were administered with 240 mL of water. Subjects refrained from lying down, eating, or drinking caffeinated beverages for 4 hours after dosing, after which a standard meal was served.

All subjects were monitored for adverse events, laboratory test abnormalities, and changes in vital signs. Blood pressure and pulse rate were measured at screening, and then prior to and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours following each dose of ziprasidone. A 12-lead electrocardiogram (ECG) reading was obtained from each person at screening and 4 hours following dosing on the days when they received 40- and 80-mg doses of ziprasidone in the fed state.

Subjects. Healthy men aged 18 and 45 years who weighed between 135 and 200 pounds (61–91 kg) were recruited. Study entry criteria specified that each subject had clinical chemistry, hematologic analyses, and urinalysis within normal ranges; a drug screen was normal; and an ethanol breath test performed on each admission to the clinical research facility was negative. In addition, all volunteers were required not to take any standard prescription drugs, over-the-counter medications, or recreational drugs for at least 2 weeks prior to participation in the study, or any investigational drugs for at least 4 weeks. Written informed consent was obtained from all participants.

Subjects were excluded if they had any condition that might affect the absorption of the drug, known drug or alcohol dependence or drug allergies, were unwilling or unable to consume a high-fat meal (e.g. vegetarians), or were smokers.

Pharmacokinetic Sampling. Blood samples were collected immediately prior to and 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 48, and 72 hours after each study drug administration to provide serum for ziprasidone concentration determination. Serum ziprasidone concentrations were determined using a validated high-performance liquid chromatography (HPLC) methodology involving liquid extraction with detection by atmospheric pressure ionization mass spectrometry. The dynamic range of the assay was linear, extended from 0.5 to 50 ng/mL, and accurate to within 5% of reference standards.

Pharmacokinetic Parameter Calculation. C_{max} (ng/mL) was estimated directly from the observed data, and the time of occurrence for the maximum concentration (T_{max}; hours) was defined as the time of the first occurrence of C_{max}. The terminal phase rate constant (K_{el}; hour^{-1}) was estimated using least squares regression analysis of the serum ziprasidone concentration–time curve during the terminal log-linear phase. The elimination half-life ($T1_{/2}$; hours) was calculated as $0.693/K_{el}$. The mean $T1_{/2}$ was estimated as 0.693/mean K_{el}.

AUC from time zero to time t of the last sample with quantifiable concentrations for ziprasidone (AUC_{0-t}; (ng hour)/mL) was estimated using linear regression trapezoidal approximation. AUC from t to infinity ($AUC_{t-\infty}$) was estimated as Cp_{est}/K_{el}, where Cp_{est} is the estimated concentration at time t based on the regression analysis. $AUC_{0-\infty}$ was estimated as the sum of AUC_{0-t} and $AUC_{t-\infty}$.

Statistical Analysis. Pharmacokinetic parameters were summarized using descriptive statistics. Means and standard deviations were calculated for $AUC_{0-\infty}$, C_{max}, and T_{max}. Means alone were calculated for $T_{1/2}$.

The relationship between $\ln(AUC_{0-\infty})$, $\ln(C_{max})$, and ln(dose) was examined by fitting a least squares regression line to each subject's fasting and fed values for $\ln(AUC_{0-\infty})$ and $\ln(C_{max})$ by dose level. The mean slopes were compared with both 0 and 1 by t test to determine whether there was a significant relationship between ln(dose) and $\ln(AUC_{0-\infty})$ and whether the relationship showed dose proportionality, respectively.

Study 2

Study Design. An open-label, nonrandomized, three-way crossover study consisting of three 3-day treatment periods was conducted in 14 healthy men or women. To minimize tolerability problems, the volunteers received ziprasidone 20 mg twice daily (bid) in the fed state for days 1–3 of the study. This was increased to ziprasidone 40 mg bid on days 4–12, with only the morning dose given on day 12. Ziprasidone capsules were used for each dose (either 1 × 20 mg bid or 1 × 40 mg bid). The three treatment periods (each 3 days in length) began on days 4, 7, and 10.

In the first treatment period, starting on day 4, the volunteers received ziprasidone 40 mg bid following consumption of a high-fat breakfast and dinner (60% of calories from fat, 25% carbohydrate, and 15% protein). In the second treatment period, the volunteers received ziprasidone 40 mg bid following consumption of moderate-fat meals (30% calories from fat, 55% carbohydrate, 15% protein). In the third treatment period, the ziprasidone 40 mg bid dose was administered in the fasted state. Up to a 5% deviation in fat content was allowed for each of the two meal types. Lunches were not controlled for distribution of calories, and the total daily calorie intake was less than 3,000 kcal.

Volunteers were confined to the research facility under continuous medical or paramedical supervision for at least 12 hours prior to day 0 through to the morning of day 13. Blood pressure and pulse rate were measured at screening and on the morning of days 1 and 12. A 12-lead ECG was performed at screening only, and laboratory tests were carried

out at screening and prior to the first dose of medication. Volunteers were monitored for adverse events throughout the study.

Subjects. The subjects for this study were healthy men or women aged 18–45 years. Each person was free of medications, including over-the-counter medications (except contraceptive medication for females of child-bearing potential). In addition, women were only enrolled if they were neither pregnant nor planning to become pregnant during the study.

Sampling. Blood samples for measurement of serum ziprasidone levels were taken immediately prior to dosing and at 1, 2, 3, 4, 6, 8, 10, and 12 hours postdose on days 3, 6, 9, and 12. Samples were also collected prior to morning and evening doses on days 4, 5, 7, 8, 10, and 11 for pharmacokinetic analysis. Serum ziprasidone was assayed using a validated HPLC assay involving solid-phase extraction and ultraviolet detection. The range limits for the assay were 1 and 250 ng/mL, respectively.

Parameter Calculation and Statistical Analysis. C_{max} for serum ziprasidone concentrations was estimated directly from the observed data. T_{max} was defined as the time for the first occurrence of C_{max}. AUC from 0 to 12 hours ($AUC_{0–12}$ for ziprasidone) was estimated using the linear trapezoidal approximation. Log-transformed AUC and C_{max} and untransformed T_{max} were analyzed using an analysis of variance, which allowed for variation due to sequence, treatment, subjects, and carryover.

RESULTS

Study 1

Eight healthy male subjects were enrolled, of which seven completed the trial (Table 1). One subject discontinued from the study due to adverse events (see later). Administration of ziprasidone immediately following consumption of a standard breakfast (a high-fat meal) led to increased systemic exposure to ziprasidone for each dose tested (Table 2 and Figure 1). Figure 1 shows the serum ziprasidone concentration as a function of time for the three doses in the fed and fasted conditions. Ziprasidone concentrations were higher in the fed than in the fasted state for any given ziprasidone dose.

Table 2 shows the data for $AUC_{0–\infty}$, C_{max}, T_{max}, and $T_{1/2}$. At the 20-, 40-, and 80-mg dose levels, mean $AUC_{0–\infty}$ for the fed treatment was 48%, 87%, and 101%, respectively, greater than with the fasted treatment. Mean C_{max} values were similar at the 20-mg dose between fed and fasted states, but were 63% and 97% greater for the fed states with the 40- and 80-mg doses, respectively. T_{max} was prolonged in the fed states for both ziprasidone 20 and 40 mg, but similar at the 80-mg dose.

TABLE 1

PARTICIPANT CHARACTERISTICS

	STUDY 1	STUDY 2	
CHARACTERISTIC	MEN (n = 8)	MEN (n = 6)	WOMEN (n = 8)
Age (years, range)	19–31 (23.7)[a]	21–42 (31.0)	20–37 (28.8)
Weight (kg, range)	68–82 (75.7)	67–83 (74.8)	51–73 (62.9)
Race (n)			
White	5	6	8
Black	1	0	0
Latin American	1	0	0
Asian	1	0	0
Discontinued (n)	1	0	2

[a]Values in parentheses indicate mean values.

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TABLE 2

PHARMACOKINETIC PARAMETERS (STUDY 1)

PARAMETER/ZIPRASIDONE DOSE	FASTED	FED
$AUC_{0-\infty}$ [mean ± SD, (ng h)/mL]		
20 mg	316 ± 110	467 ± 105
40 mg	481 ± 187	902 ± 263
80 mg	950 ± 329	1911 ± 548
C_{max} (mean ± SD, ng/mL)		
20 mg	46 ± 16	50 ± 8
40 mg	54 ± 28	87 ± 26
80 mg	84 ± 32	165 ± 33
T_{max} ± SD (hours)		
20 mg	4.1 ± 1.4	5.6 ± 2.8
40 mg	4.4 ± 1.5	6.4 ± 3.6
80 mg	6.0 ± 3.2	6.6 ± 2.8
Mean $T_{1/2}$ (hours)		
20 mg	4.7	3.8
40 mg	6.8	4.1
80 mg	6.2	3.7

$AUC_{0-\infty}$, total area under the serum concentrationtime curve; C_{max}, maximum drug concentration; T_{max}, time of occurrence for the maximum concentration; $T_{1/2}$, elimination half-life.

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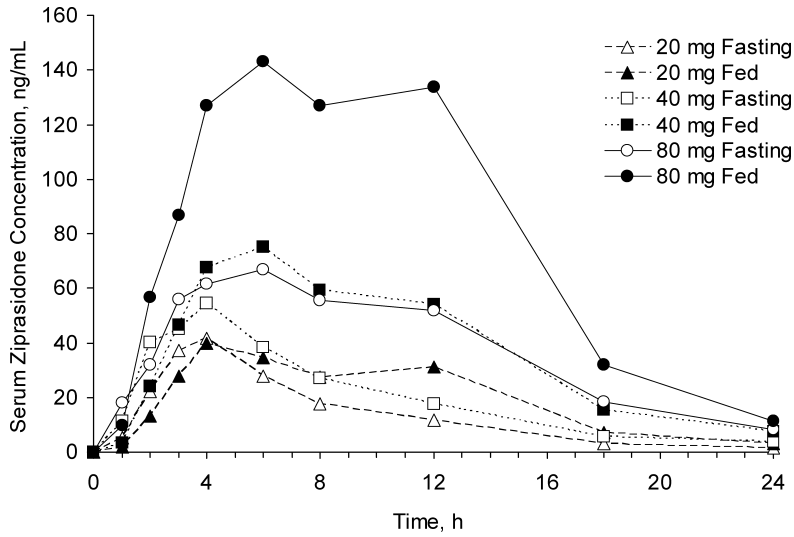
Ziprasidone had a shorter $T1/2$ in the fed than in the fasted state. These values correspond to a 19%, 40%, and 40% decrease in the mean $T1/2$ for ziprasidone 20-, 40-, and 80-mg doses, respectively, in the fed versus the fasted state.

The mean within-subject slope of $\ln(AUC_{0-\infty})$ versus dose level in the fasting condition was 0.77 and was significantly different from both

FIGURE 1

MEAN SERUM ZIPRASIDONE CONCENTRATIONS POSTDOSE IN FED AND FASTING SUBJECTS AFTER A SINGLE ORAL DOSE OF ZIPRASIDONE 20, 40, OR 80 MG (STUDY 1).



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zero ($P = .0001$) and 1 ($P = .0351$), indicating that an increase in ziprasidone dose under fasting conditions resulted in a less than proportional increase in $\ln(AUC_{0-\infty})$. By contrast, the within-subject slope was 1.03 in fed subjects. This was significantly different from zero ($P = .0001$) but was not significantly different from 1 ($P = .6448$), indicating that an increase in ziprasidone under fed conditions resulted in a dose-proportional increase in $\ln(AUC_{0-\infty})$.

The difference between the mean fed $\ln(C_{max})$ and the mean fasting $\ln(C_{max})$, irrespective of ziprasidone dose, was significantly different from zero ($P = .0044$), thus showing a significant relationship between $\ln(C_{max})$ and fasting status.

Safety. One subject discontinued the study after receiving ziprasidone 80 mg in the fasted state and reporting nausea and restlessness of moderate intensity that was thought to be treatment-related. All reported adverse events were considered by the investigator to be possibly related to treatment and were mild to moderate in severity; the incidence and severity of treatment-emergent adverse events increased with increasing dose and were generally more frequent under fed conditions at each dose level. The most frequently reported adverse event was somnolence; others included dizziness, agitation, headache, diarrhea, nausea, and vomiting.

No clinically significant laboratory tests abnormalities were reported. Several subjects experienced decreases in supine blood pressure within 8 hours following single doses of ziprasidone; however, there was no dose dependency of the effect among the subjects. No abnormalities or significant changes in ECG results were observed for any subject.

Study 2

Fourteen subjects (six male) entered this study (Table 1) of which two discontinued. One participant permanently discontinued due to adverse events (see later). Both fed states (60%- and 30%-fat meals) produced substantial increases in ziprasidone absorption compared with the fasting condition (Figure 2 and Table 3). For example, the mean $AUC_{(0–12)}$ was 104% and 79% greater for the 60%- and 30%-fat meals, respectively, than in fasting subjects. A direct comparison of the bioavailability (i.e., AUC) of ziprasidone between the 60%- and 30%-fat meals did not show any significant difference: the ratio of AUC values for medium-fat and high-fat meals was 87.8%. Similarly, mean C_{max} was 84% and 98% higher in subjects who received ziprasidone with a 60%-fat or 30%-fat containing meal, respectively.

For both $AUC_{(0–12)}$ and C_{max}, variability was reduced in the presence of moderate- or high-fat meals as evident from an approximate 50%

FIGURE 2

MEAN SERUM ZIPRASIDONE CONCENTRATIONS POSTDOSE AS A FUNCTION OF TIME AFTER AN ORAL DOSE OF ZIPRASIDONE 40 MG IN FASTING SUBJECTS AND THOSE RECEIVING MODERATE- OR HIGH-FAT MEALS (STUDY 2).

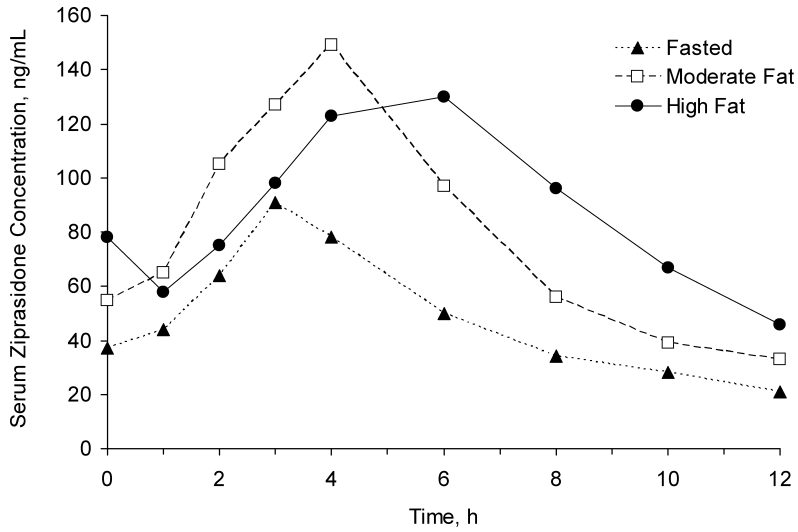

TABLE 3

PHARMACOKINETIC RESULTS (STUDY 2)

	FASTED (F)	MODERATE FAT (MF)	HIGH FAT (HF)	COMPARISON	RATIO (%)/ DIFFERENCE[a]
N	13	12	13		
$AUC_{(0-12)} \pm SD$ [(ng h)/mL])	538 ± 218 (41)[b]	940 ± 215 (23)	1067 ± 209 (20)	MF vs. F MF vs. HF HF vs. F	179.2 [156.1–205.7][c] 87.8 [76.4–100.8] 204.2 [178.9–233.1]
$C_{max} \pm SD$ (ng/mL)	86 ± 44 (51)	163 ± 36 (22)	152 ± 32 (21)	MF vs. F MF vs. HF HF vs. F	197.7 [168.1–232.6] 107.7 [91.5–125.8] 183.6 [157.1–214.5]
$T_{max} \pm SD$ (hours)	2.8 ± 0.9	3.4 ± 1.3	5.1 ± 1.9	MF vs. F MF vs. HF HF vs. F	0.8 [−0.2 to 1.8] −1.5 [−2.4 to −0.5] 2.3 [1.3–3.2]

All patients received ziprasidone 40 mg bid.
AUC_{0-12}, area under the serum concentration–time curve from 0 to 12 hours; CV%, coefficient of variation (%); C_{max}, maximum drug concentration; T_{max}, time of occurrence for the maximum concentration.
[a]Ratio of geometric mean values shown for AUC and C_{max}; difference of arithmetic mean values shown for T_{max}.
[b]Values in parentheses indicate CV%s.
[c]Values in square brackets indicate 90% confidence limits.

decrease in the percentage coefficient of variation relative to fasting subjects.

Predose evening concentrations of ziprasidone were approximately one-third lower than in the morning, regardless of meal type or fed versus fasted state.

Safety. The majority of adverse events in the study were mild or moderate in severity, and the most frequently reported were dizziness and insomnia. Ten subjects experienced 11 severe adverse events that were attributed to study drug by the investigator. These included (experienced by one subject for each regimen except as noted): dizziness, sweating, anxiety, insomnia (two subjects), and dyspnea with the 40-mg bid high-fat food regimen; headache (two subjects), anxiety, dizziness, syncope, sweating, and nausea with the 40-mg bid moderate-fat regimen; sweating, abnormal dreams, anxiety, insomnia, abdominal pain, and dry mouth with the 40-mg bid fasted regimen.

Two subjects discontinued the study. One subject permanently discontinued due to severe syncope on day 12, judged to be treatment related by the investigator. After lying supine with legs elevated, she recovered the same day with no additional intervention.

No laboratory abnormalities were reported during the study.

DISCUSSION

Food effects on the oral bioavailability of drugs are complex and multifactorial—the influences include the extent of drug solubilization and modification of gastric transit times.[8] Most food effect studies in the clinical literature focus on the effects of an FDA standard meal. The composition of this meal is high in fat and probably unrepresentative of diets used outside research environments. This study examined the effects of a range of ziprasidone doses and two different meal compositions.

Overall, systemic exposure to ziprasidone was greater and proportional to dose when doses of 20, 40, and 80 mg were administered under fed conditions. Under fasting conditions, the increases in AUC and C_{max} were less than dose proportional; under fed conditions, they were dose proportional.

The fed versus fasting results from study 1 are echoed in the results of study 2, in which the administration of a meal enhanced ziprasidone drug bioavailability. AUC values for ziprasidone after a moderate- or high-fat meal were increased 1.8- and 2-fold, respectively, relative to those observed under fasting conditions. Conversely, C_{max} values were slightly larger in the moderate-fat meal group than in the high-fat condition. Overall, the reduction in the fat content of the food (from 60% to 30% fat) had no notable affect on ziprasidone bioavailability.

The absence of any greater effect with high-fat relative to moderate-fat meals suggests that, although ziprasidone is lipophilic, the amount of fat present in the medium-fat meal is sufficient for drug absorption. There was less pharmacokinetic variability observed in the fed state than in the fasted state, suggesting more consistent absorption of ziprasidone when it is taken with food. This may be due to improved dissolution of ziprasidone in the presence of food, as found for other drugs.[9]

The increase in frequency and severity of adverse events in the fed versus fasting states at the same dose level is consistent with the observed pharmacokinetics of ziprasidone in this study, reflecting an increase in systemic exposure with increasing dose and greater exposure under fed versus fasting conditions for all dose levels.

Collectively, these data confirm previous studies[6] that show food to enhance the bioavailability of ziprasidone with food and ensure dose-related increases in exposure. In conclusion, these studies reinforce previous findings that ziprasidone should be taken with food to ensure optimal absorption and linear pharmacokinetics. The fat content of the food does not appear to be a major determinant of ziprasidone bioavailability. Food will also provide more consistent daily systemic exposure to ziprasidone and, thus, better symptom control and tolerability. ✤

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