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RESEARCH PAPER

# Improved Ziprasidone Formulations with Enhanced Bioavailability in the Fasted State and a Reduced Food Effect

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## ABSTRACT

***Purpose*** To develop and characterize new formulations of ziprasidone with a reduced food effect achieved by increasing exposure in the fasted state.

***Methods*** Formulations were developed utilizing the following solubilization technologies: inclusion complex of ziprasidone mesylate and cyclodextrin, ziprasidone free base nano-suspension, and semi-ordered ziprasidone HCl in polymer matrix. Pharmacokinetic studies were conducted with these formulations to examine the bioavailability of test formulations in fasted and fed state compared to commercial capsules (Geodon®) dosed in the fed state.

***Results*** All formulations containing solubilized ziprasidone showed either no food effect or a reduced food effect compared to commercial capsules. Two formulations when taken in the fasted or fed state were comparable to the commercial capsules dosed in the fed state with respect to total exposure. However, peak concentrations were ~30–40% higher.

***Conclusions*** Pharmacokinetic studies indicated solubilization technologies can be employed to successfully increase the extent of ziprasidone absorption in the fasted state, thereby reducing the food effect. Such formulations could provide simple and convenient dosing while retaining the familiar safety and efficacy profile of currently marketed capsules.

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## INTRODUCTION

Ziprasidone (5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one], a dopamine ($D_2$) receptor antagonist, is an orally active atypical antipsychotic drug used in the treatment of schizophrenia and bipolar disorder (1,2). It is commercially marketed worldwide under the brand names of Geodon® or Zeldox®. The absorption of ziprasidone is increased up to two-fold in the presence of food (3,4), and administration with food is considered crucial to ensure optimal, reliable, dose-dependent bioavailability, and thus predictable symptom control and tolerability (5). Studies have shown that the calories consumed (should be greater than 500 kcal irrespective of the fat content) and time between dosing and food intake (should be less than 2 h) are important factors in the absorption of ziprasidone (6,7). It has been noted that "the reduced oral absorption of ziprasidone in the fasted state cannot be compensated for by increasing the prescribed dose" (8,9).

Although the dosing and administration instructions for Geodon require patients to take the medication with food (10), around 50% of patients with schizophrenia do not fully comply with treatment, and noncompliance is linked to relapse, re-hospitalization, poor outcome, and high economic costs (11). Market research (Idedics. Primary FF market research, Pfizer Inc., 2007) has indicated that about 25% of physicians do not instruct patients to take Geodon with food, and ~50% of the physicians instruct their patients to take Geodon with a snack without specifying a caloric content. The report also concluded that about 40% of the patients did not take at least half of

their weekly Geodon doses with sufficient "calories." In another market research study (Putnam Associates, STEP Study, Pfizer Inc., 2008), physicians estimated that 40–60% of their patients do not consistently take Geodon with sufficient food, and 45–85% of physicians perceived therapeutic response to Geodon to be less effective in patients who take it with insufficient calories of food. Experts have also noted that poor compliance with treatment of any type is an issue for patients with schizophrenia, and compliance with a complex medication regimen, e.g., twice daily dosing and dosing with food, is likely to be worse (12).

A ziprasidone formulation with no food effect or with a reduced food effect such that it can be taken without regard to food should logically result in more consistent drug levels in the blood and has the potential to enhance response uniformity in a poorly compliant patient population. Some other possible advantages of such a new formulation are as follows: (a) the new formulation taken with or without food would be able to achieve a $D_2$ receptor occupancy consistent with antipsychotic efficacy, while Geodon capsules taken without food may not achieve this; (b) the new formulation may be a beneficial option for the ~40% of patients who do not take their Geodon with sufficient calories; (c) in patients at risk of weight gain and its associated health complications, the new formulation would take advantage of the benign metabolic profile of ziprasidone while adding greater flexibility in managing daily caloric intake; (d) the new formulation would provide the familiar safety and tolerability profile of Geodon without the burden of taking it with at least a 500-calorie meal to achieve the target absorption; (e) the new formulation would provide a means to more reliably titrate the dose to achieve the desired effect independent of patient compliance (i.e., consistent with FDA guidance to treat patients with the lowest efficacious dose); and (f) the new formulation would provide simple and convenient dosing, thereby increasing patient compliance, as it would be easier to administer at 12-h intervals, since dosing is not tied to meal times.

Food-drug interactions resulting in altered pharmacokinetics are well known (13,14). Food can result in delayed, decreased, increased, or unchanged absorption. Several mechanisms can contribute to increased drug absorption when administered with food, including increased solubilization. Ziprasidone is a poorly water-soluble (free base solubility in water = 0.3 μg/mL) and a highly lipophilic compound ($c$ log $P$ = 3.6). We hypothesized that the food effect of ziprasidone is related to increased absorption due to increased solubilization and/or increased rate of dissolution from the dosage form in the presence of food. Therefore, solubilized forms of ziprasidone or forms exhibiting an increased rate of dissolution could eliminate or reduce its food effect.

Numerous technologies are available for increasing the absorption of poorly water-soluble drugs including prodrugs (15,16), new salts (17), crystal engineering (18), lipid-based delivery systems (19–21), cyclodextrin-based inclusion complexes (22), nanosizing (23,24), and hydroxypropyl methylcellulose acetate succinate-based spray dried dispersions (25).

In this study, we investigated the pharmacokinetics and food effect of the following solubilized forms of ziprasidone: (1) a ziprasidone mesylate-SBECD inclusion complex, (2) a ziprasidone free base nano-suspension, and (3) a semi-ordered ziprasidone HCl in an HPMCAS matrix.

## MATERIALS AND METHODS

### Materials

Ziprasidone free base, mesylate and hydrochloride salts were obtained from Pfizer, Inc. Sulfobutyl ether β-cyclodextrin sodium (SBECD) was manufactured by Pfizer Inc. under license purchased from CyDex Pharmaceuticals, Inc. (Lenexa, KS). Hypromellose acetate succinate AQOAT®, referred to in this paper by its older name, Hydroxypropyl methylcellulose acetate succinate (HPMCAS), Poloxamer 338 (Pluronic® F108), Polysorbate 80 (Tween® 80), Soybean lecithin, Methacrylic Acid Copolymer Type C (Eudragit L100-55), Microcrystalline cellulose (Avicel® PH102 and Avicel® PH200), Lactose monohydrate (Fast Flo 316), Crospovidone (Polyplasdone XL), and Magnesium stearate were compendial grade and obtained through the Inventory Management group at Pfizer Inc. All other chemicals, reagents, and solvents were analytical grade and were purchased from commercial suppliers by Pfizer Inc.

### Test Formulation A

A ziprasidone mesylate-SBECD inclusion complex containing 117.0 mg ziprasidone (anhydrous)/g of powder was prepared by bulk freeze drying a solution of SBECD and the drug followed by milling the milled lyophilized powder (26). The lyophilized powder was then mixed with HPMCAS (MF grade) in the mass ratio of approximately 7:2 and filled into a gelatin capsule. Each capsule contained the equivalent of 20 mg ziprasidone, and two capsules were administered to obtain a 40 mg dose of ziprasidone.

### Test Formulation B

A 210 mg/mL ziprasidone free base nano-suspension was prepared by wet-milling at 2100 RPM for 30 min using

Nanomill-1™ (Manufacturer: Elan Drug Delivery, Inc., King of Prussia, PA). The grinding media consisted of 500 μm size polystyrene beads. Poloxamer 338 (Pluronic® F108), Polysorbate 80 (Tween® 80) and Soybean Lecithin were used as surface stabilizers/surface modifiers. The nanosuspension was prepared at 4°C at 2100 RPM. The resulting suspension was filtered under vacuum to remove the milling media (27). An appropriate volume of the suspension (0.19 mL corresponding to 40 mg dose of ziprasidone) was diluted in 60 mL water and administered as a suspension.

### Test Formulation C

A form of ziprasidone consisting of semi-ordered ziprasidone HCl in an HPMCAS matrix (28), referred to as ziprasidone HCl crystallized spray-dried dispersion (CSDD), was prepared by spray drying a solution of ziprasidone HCl and HPMCAS (HG grade) (1:4 ratio by weight) in methanol, drying the resulting spray-dried dispersion (SDD) in a conventional tray drier, and then exposing the SDD to 50°C and 90%RH for 24 h. Immediate release tablets containing ziprasidone HCl CSDD (35.6% by weight loading), microcrystalline cellulose, lactose, crospovidone, and magnesium stearate were made so that each tablet contained 40 mg of ziprasidone.

### Test Formulation D

Ziprasidone HCl CSDD was prepared as described above for test Formulation C. Ziprasidone HCl CSDD modified release (MR) granules were prepared by an extrusion granulation process using ziprasidone HCl CSDD and Methacrylic Acid Copolymer Type C (Eudragit L100-55) (3:2 ratio by weight) with ethanol/water at ambient temperature.

Immediate release tablets containing ziprasidone HCl CSDD (35.6% by weight loading), microcrystalline cellulose, lactose, crospovidone, and magnesium stearate were prepared by a conventional roller compaction process so that each tablet contained 24 mg of ziprasidone. Tablets containing ziprasidone HCl CSDD MR granules (40% by weight loading), microcrystalline cellulose, crospovidone, and magnesium stearate were made so that each tablet contained 16 mg of ziprasidone.

Test Formulation D consisted of dosing one tablet containing ziprasidone HCl IR granules (24 mg) and one tablet containing ziprasidone HCl MR granules (16 mg) for a total dose of 40 mg ziprasidone.

### Pharmacokinetic Evaluations

The pharmacokinetic studies were randomized, open-label, crossover studies to examine the bioavailability of Geodon commercial capsule under fed conditions and of a test ziprasidone dosage form (Formulations A, B, or D) under fed and fasted conditions, all after single 40 mg doses. All subjects were healthy, with a BMI of approximately 18 to 30 kg/m$^2$ and a total body weight>50 kg. Subjects were randomized to one of six treatment sequences on Day 1 of Period 1. Each treatment period was separated by a

**Table I** Summary of the Pharmacokinetic Studies

| Formulation | Description | Number of subjects | Number of subjects completing study treatments | | |
|---|---|---|---|---|---|
| | | | A fasted | A fed | Commercial capsule fed |
| A | Ziprasidone mesylate-SBECD complex | 16 | 12 | 15 | 13 |
| | | | B fasted | B fed | Commercial capsule fed |
| B | Ziprasidone free base nanosuspension | 14 | 12 | 12 | 12 |
| | | | C fasted | C fed | Commercial capsule fed |
| C | Ziprasidone HCl CSDD | 18 | 17 | | 17 |
| | Ziprasidone HCl CSDD | 24 | | 23 | 24 |
| | | | D fasted | D fed | Commercial capsule fed |
| D | Ziprasidone HCl (CSDD IR granules + CSDD MR granules) | 20 | 20 | 19 | 20 |
| | | | Commercial capsule fasted | Commercial capsule fed | |
| Commercial capsules[a] | Ziprasidone HCl commercial IR capsules | 8 | 8 | 8 | |

[a] Historical fed-fasted data with commercial capsules was used for comparison of the performance of the test formulations and in the pharmacokinetic simulations.

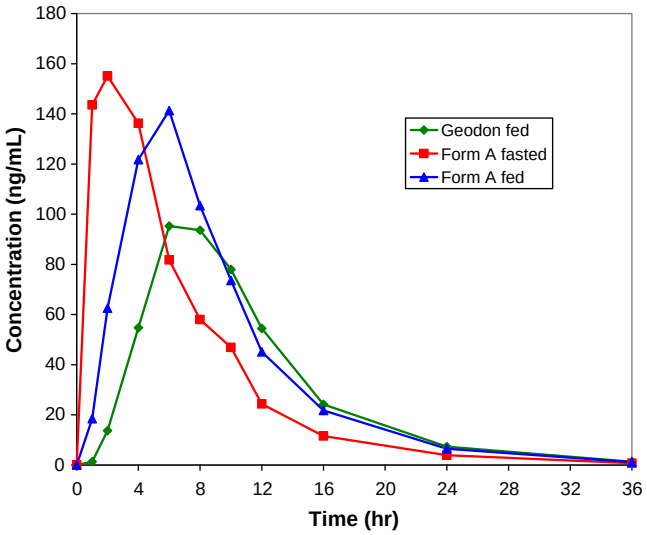


**Fig. 1** Mean serum ziprasidone concentrations in healthy volunteers following 40 mg oral doses of Geodon® capsules in the fed state and Formulation A in the fasted and fed state.

minimum three-day washout interval. Written informed consent was obtained from all study subjects, and the study protocols were approved by the Institutional Review Board. In the case of Formulation C, there were two pharmacokinetic separate studies, one which studied Formulation C in the fasted state and another which studied Formulation C in the fed state. Both studies had a control arm of Geodon given in the fed state.

For the test formulation (fasted) treatment, subjects were administered the drug with 240 mL of water following an overnight fast of at least 10 h. In the case of the test formulation (fed) and commercial capsule (fed) treatments, following an overnight fast of at least 10 h, subjects were provided with a standardized high-calorie/high-fat breakfast, consisting of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, and eight ounces of whole milk. The breakfast was consumed over a 20-min period, with the drug administered within 5 min after completion of the meal with 240 mL of water.

For both the fasted and fed treatments, no food was allowed for at least 4 h post-dose. Water was allowed as desired except for 1 h before and after drug administration. A standard lunch was provided about 4 h after dosing and dinner about 10 h after dosing. An evening snack was permitted on the day of dosing.

Blood samples (5 mL) were collected at the following times: pre-dose, and 1, 2, 4, 6, 8, 10, 12, 16, 24, and 36 h after drug administration. The serum samples were assayed for ziprasidone using a validated liquid chromatography/dual mass spectrometry (LC/MS/MS) assay (29).

Because Geodon capsules were studied only in the fed state in this series of pharmacokinetic studies, available historical fed-fasted data with Geodon capsules (30) are used for comparison of the performance of the test formulations and in the pharmacokinetic simulations.

The pharmacokinetic studies were not powered for bioequivalence. However, in analyzing the similarity of $AUC_{inf}$ and $C_{max}$ ratios, we considered the commonly used criteria for bioequivalence by the U.S. Food and Drug Administration, i.e., 90% Confidence Intervals (CIs) between 0.80 and 1.25 (31). In analyzing the food effect in individual subjects, we considered ratios between 0.80 and

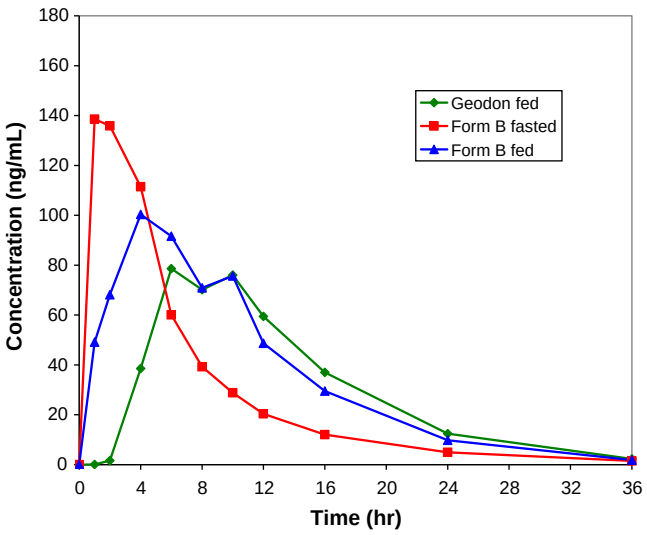


**Fig. 2** Mean serum ziprasidone concentrations in healthy volunteers following 40 mg oral doses of Geodon® capsules in the fed state and Formulation B in the fasted and fed state.

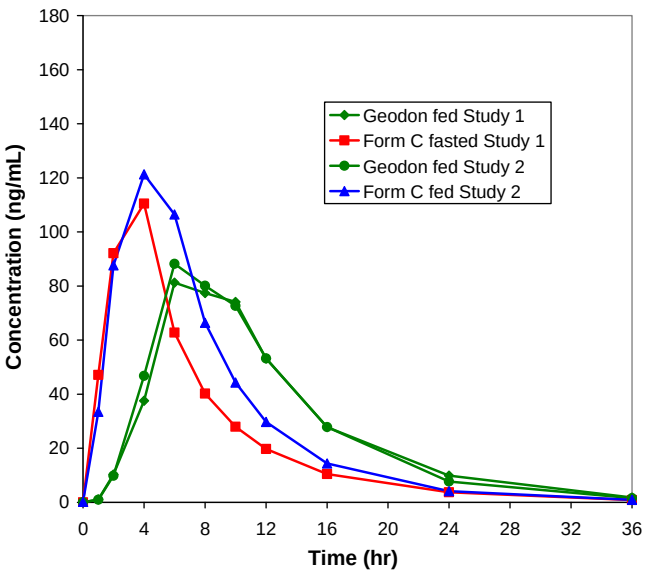


**Fig. 3** Mean serum ziprasidone concentrations in healthy volunteers following 40 mg oral doses of Geodon® capsules in the fed state and Formulation C in the fasted and fed state.

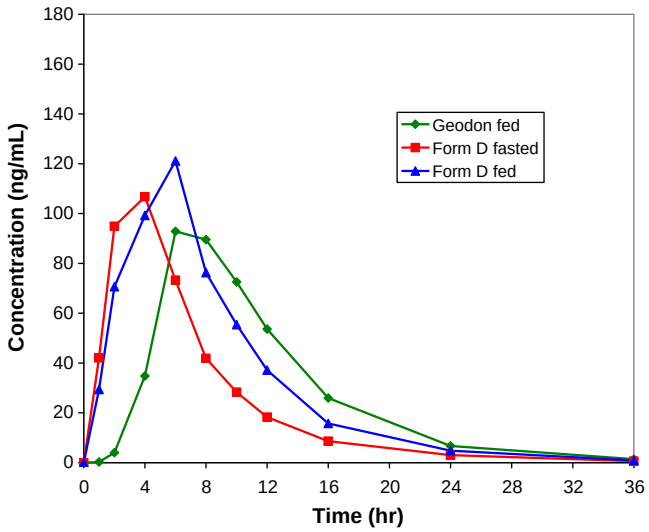


**Fig. 4** Mean serum ziprasidone concentrations in healthy volunteers following 40 mg oral doses of 40 mg Geodon® capsules in the fed state and Formulation D in the fasted and fed state.

1.25 and 0.70–1.43 to correspond to a no food effect and a moderate food effect, respectively. The wider limits have a statistical basis (32–37) and have sometimes been considered as appropriate bioequivalence criteria for highly variable drugs. The wider limits were once considered for $C_{max}$ in a draft guidance on evaluating food effects (38).

## Statistical Methods

The pharmacokinetic parameters were calculated for each subject for each treatment using standard non-compartmental analysis of concentration-time data. The precision of the estimate of pharmacokinetic parameters ($AUC_{inf}$ and $C_{max}$) was determined by constructing 90% CIs around the estimated difference between the Test and Reference treatments using a mixed effects model based on natural log transformed data. The mixed effects model was implemented using SAS Proc Mixed, with REML estimation method and Kenward-Roger degrees of freedom algorithm.

## Statistical Analysis

The natural log-transformed pharmacokinetic parameters were analyzed using a mixed effects model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

## Pharmacokinetic Simulations

The steady-state concentration *versus* time profiles for Geodon capsules and selected test formulations in the fasted and fed state were simulated from single dose data using the principle of superposition. The simulations generated using the non-compartmental superposition tools in WinNonlin 3.2 (Pharsight Corporation, Mountain View, CA) were comparable to those generated using MATLAB (MathWorks, Natick, MA).

To illustrate the benefits of a ziprasidone formulation with a reduced food effect, the steady-state concentration *versus* time profiles were also simulated for compliant, non-compliant, and partially compliant patients taking Geodon or Formulation D. Although non-compliance and partial compliance in the context of Geodon dosing can take a variety of forms, such as not taking medicine with the recommended amount of food, delaying or skipping doses, etc., we assumed that compliant patients always take their medication with

**Table II** Statistical Summary of Treatment Comparisons (Formulation A)

| Parameter (Units) | Comparisons | Adjusted Geometric Mean (AGM) | | Ratio (%) of AGM (Test/Reference) | 90% CI Ratio (%) |
|---|---|---|---|---|---|
| | | Test | Reference | | |
| $AUC_{inf}$ (ng.h.mL) | Formulation A (Fasted) *vs* Geodon (Fed) | 1183.69 | 1164.04 | 101.69 | (95.40, 108.39) |
| | Formulation A (Fed) *vs* Geodon (Fed) | 1281.71 | 1164.04 | 110.00 | (103.31, 117.35) |
| | Formulation A (Fed) *vs* Formulation A (Fasted) | 1281.71 | 1183.69 | 108.28 | (101.81, 115.16) |
| $C_{max}$ (ng/mL) | Formulation A (Fasted) *vs* Geodon (Fed) | 179.58 | 119.96 | 149.70 | (126.81, 176.72) |
| | Formulation A (Fed) *vs* Geodon (Fed) | 160.09 | 119.96 | 133.45 | (113.27, 157.23) |
| | Formulation A (Fed) *vs* Formulation A (Fasted) | 160.09 | 179.58 | 89.15 | (75.85, 104.77) |

**Table III** Statistical Summary of Treatment Comparisons (Formulation B)

| Parameter (Units) | Comparisons | Adjusted Geometric Mean (AGM) | | Ratio (%) of AGM (Test/Reference) | 90% CI Ratio (%) |
|---|---|---|---|---|---|
| | | Test | Reference | | |
| $AUC_{inf}$ (ng.h.mL) | Formulation B (Fasted) *vs* Geodon (Fed) | 959.97 | 1090.74 | 88.01 | (75.33, 102.83) |
| | Formulation B (Fed) *vs* Geodon (Fed) | 1243.87 | 1090.74 | 114.04 | (97.50, 133.38) |
| | Formulation B (Fed) *vs* Formulation B (Fasted) | 1243.87 | 959.97 | 129.57 | (110.91, 151.38) |
| $C_{max}$ (ng/mL) | Formulation B (Fasted) *vs* Geodon (Fed) | 151.15 | 98.86 | 152.90 | (120.01, 194.80) |
| | Formulation B (Fed) *vs* Geodon (Fed) | 111.85 | 98.86 | 113.15 | (88.45, 144.74) |
| | Formulation B (Fed) *vs* Formulation B (Fasted) | 111.85 | 151.15 | 74.00 | (58.08, 94.28) |

food, non-compliant patients take it without food and partially compliant patients take the morning dose in the fasted state and the evening dose in the fed state. It should also be noted that, for these simulations, we used the single dose data from healthy volunteers *versus* patients. This is justified as there are no known pharmacokinetic differences for the two populations and the target illness would not be expected to affect the hepatically based metabolism of ziprasidone.

The concentration *versus* time profile for higher (and lower) doses of Formulation D was simulated from the 40 mg data assuming dose linearity. The 80 mg profile was compared to the concentration *versus* time profile following intramuscular dosing.

## RESULTS

### Pharmacokinetic Studies

A summary of the formulations tested and the number of subjects assigned to and completing the treatments in each of the pharmacokinetic studies is given in Table I. Also included in Table I is a historical fed-fasted pharmacokinetic study with the commercial Geodon capsules.

The mean serum ziprasidone concentrations after administration of the test formulations in the fed and fasted state and Geodon administered in the fed state are shown in Figs. 1, 2, 3 and 4, and the results from the statistical analyses of the treatment comparisons are summarized in Tables II, III, IV and V. Some highlights from the pharmacokinetic studies for each of the test formulations are given below.

#### *Formulation A*

When Formulation A (fasted) was compared to Geodon (fed), a similar extent ($AUC_{inf}$) but greater rate of absorption (higher $C_{max}$ and earlier $T_{max}$) was observed. A comparison of Formulation A (fed) to Formulation A (fasted) suggested the absence of a significant food effect on $AUC_{inf}$ or $C_{max}$.

#### *Formulation B*

When Formulation B (fasted) was compared to Geodon (fed), a marginally lower extent ($AUC_{inf}$) but substantially greater rate of absorption (higher $C_{max}$ and earlier $T_{max}$) was observed. Comparing the test formulation given in the fed and fasted states, the results indicated a significant positive

**Table IV** Statistical Summary of Treatment Comparisons (Formulation C)

| Parameter (Units) | Comparisons | Adjusted Geometric Mean (AGM) | | Ratio (%) of AGM (Test/Reference) | 90% CI Ratio (%) |
|---|---|---|---|---|---|
| | | Test | Reference | | |
| $AUC_{inf}$ (ng.h.mL) | Formulation C (Fasted) *vs* Geodon (Fed) | 794.11 | 864.54 | 91.85 | (78.90, 106.93) |
| | Formulation C (Fed) *vs* Geodon (Fed) | 1021.71 | 955.73 | 106.90 | (101.82, 112.24) |
| | Formulation C (Fed) *vs* Formulation C (Fasted) | Comparison not possible | | | |
| $C_{max}$ (ng/mL) | Formulation C (Fasted) *vs* Geodon (Fed) | 123.76 | 92.25 | 134.17 | (114.74, 156.89) |
| | Formulation C (Fed) *vs* Geodon (Fed) | 158.76 | 102.40 | 155.05 | (139.07, 172.85) |
| | Formulation C (Fed) *vs* Formulation C (Fasted) | Comparison not possible | | | |

**Table V** Statistical Summary of Treatment Comparisons (Formulation D)

| Parameter (Units) | Comparisons | Adjusted Geometric Mean (AGM) | | Ratio (%) of AGM (Test/Reference) | 90% CI Ratio (%) |
|---|---|---|---|---|---|
| | | Test | Reference | | |
| $AUC_{inf}$ (ng.h.mL) | Formulation D (Fasted) *vs* Geodon (Fed) | 800.36 | 917.82 | 87.20 | (82.67, 91.99)Z |
| | Formulation D (Fed) *vs* Geodon (Fed) | 1045.19 | 917.82 | 113.88 | (108.07, 120.00) |
| | Formulation D (Fed) *vs* Formulation D (Fasted) | 1045.19 | 800.36 | 130.59 | (123.81, 137.74) |
| $C_{max}$ (ng/mL) | Formulation D (Fasted) *vs* Geodon (Fed) | 133.04 | 103.02 | 129.15 | (114.41, 145.78) |
| | Formulation D (Fed) *vs* Geodon (Fed) | 135.29 | 103.02 | 131.33 | (116.60, 147.92) |
| | Formulation D (Fed) *vs* Formulation D (Fasted) | 135.29 | 133.04 | 101.69 | (90.10, 114.77) |

food effect on $AUC_{inf}$ and negative food effect on $C_{max}$. None of these comparisons met the standard bioequivalence criteria, i.e., 90% CI within 80–125%.

### *Formulation C*

Compared to Geodon (fed), Formulation C (fasted or fed) was more rapidly absorbed, resulting in a higher $C_{max}$ and an earlier Tmax. Formulation C showed an approximately 10% lower extent of absorption in the fasted state but marginally increased extent of absorption compared to Geodon in the fed state. A direct assessment of the food effect for Formulation C was not possible because the fasted and fed data came from two different clinical studies.

### *Formulation D*

Compared with Geodon capsules (fed), Formulation D appeared to provide higher peak concentrations ($C_{max}$) under both the fed and fasted conditions. There was a 12.8% decrease in the extent of absorption ($AUC_{inf}$) with Formulation D compared to Geodon (fed), while $C_{max}$ was increased by approximately 29%. In the fed state, the $AUC_{inf}$ and $C_{max}$ increased by approximately 14% and 31%, respectively, when compared to Geodon (fed). For food effect assessment, a comparison of exposure with Formulation D under fed *versus* fasting conditions showed an increase with food of 31% for $AUC_{inf}$ and virtually no change in $C_{max}$.

**Table VI** Intra-subject Food Effect for AUC and $C_{max}$ for Formulation D Compared to Geodon

| Formulation D (40 mg) | | | Geodon capsules (40 mg) | | |
|---|---|---|---|---|---|
| Subject | $AUC_{inf}$ ratio (Fed/Fasted) | $C_{max}$ ratio (Fed/Fasted) | Subject | $AUC_{inf}$ ratio (Fed/Fasted) | $C_{max}$ ratio (Fed/Fasted) |
| 2 | 1.54 | 1.31 | 1 | 1.83 | 2.39 |
| 3 | 1.25 | 0.98 | 2 | 2.21 | 1.17 |
| 4 | 1.22 | 1.08 | 3 | 1.39 | 0.70 |
| 5 | 1.12 | 0.81 | 4 | 1.18 | 1.04 |
| 6 | 1.15 | 0.48 | 5 | 2.32 | 2.01 |
| 7 | 1.89 | 1.98 | 6 | 1.79 | 1.61 |
| 8 | 1.28 | 1.32 | 7 | 2.51 | 2.59 |
| 9 | 1.22 | 1.07 | 8 | 2.17 | 2.87 |
| 10 | 1.32 | 1.11 | | | |
| 11 | 1.44 | 1.20 | | | |
| 12 | 1.47 | 1.26 | | | |
| 13 | 1.13 | 0.80 | | | |
| 14 | 1.27 | 0.95 | | | |
| 15 | 1.28 | 1.17 | | | |
| 16 | 1.13 | 0.82 | | | |
| 17 | 1.17 | 0.88 | | | |
| 18 | 1.41 | 1.01 | | | |
| 19 | 1.25 | 0.80 | | | |
| 20 | 1.65 | 1.07 | | | |

Color code for the cells: Green = ratio between 0.80 and 1.25 (no food effect), Yellow = ratio between 0.70 and 1.43 (moderate food effect), and Red = ratio less than 0.70 or greater than 1.43 (food effect).

**Table VII** Individual $AUC_{inf}$ and $C_{max}$ Ratios of Pharmacokinetic Parameters for Formulation D

| | Formulation D fasted/Geodon fed | | Formulation D fed/Geodon fed | |
|---|---|---|---|---|
| Subject | $AUC_{inf}$ ratio | $C_{max}$ ratio | $AUC_{inf}$ ratio | $C_{max}$ ratio |
| 1 | | | 0.86 | 0.98 |
| 2 | 0.89 | 1.06 | 1.37 | 1.39 |
| 3 | 1.03 | 3.44 | 1.29 | 3.36 |
| 4 | 0.98 | 1.16 | 1.20 | 1.25 |
| 5 | 0.92 | 1.24 | 1.03 | 1.01 |
| 6 | 0.87 | 2.65 | 1.00 | 1.28 |
| 7 | 0.56 | 0.71 | 1.06 | 1.41 |
| 8 | 1.02 | 1.55 | 1.30 | 2.04 |
| 9 | 1.02 | 1.18 | 1.24 | 1.26 |
| 10 | 0.75 | 1.14 | 1.00 | 1.27 |
| 11 | 0.88 | 1.13 | 1.27 | 1.36 |
| 12 | 0.88 | 1.06 | 1.29 | 1.33 |
| 13 | 1.10 | 1.38 | 1.25 | 1.10 |
| 14 | 0.82 | 1.14 | 1.04 | 1.08 |
| 15 | 0.84 | 1.33 | 1.07 | 1.56 |
| 16 | 0.91 | 1.19 | 1.03 | 0.98 |
| 17 | 0.96 | 1.23 | 1.13 | 1.08 |
| 18 | 0.84 | 1.54 | 1.18 | 1.56 |
| 19 | 0.93 | 1.53 | 1.16 | 1.22 |
| 20 | 0.70 | 0.97 | 1.16 | 1.03 |

Color code for the cells: Green = ratio between 0.80 and 1.25, Yellow = ratio between 0.70 and 1.43, and Red = ratio less than 0.70 or greater than 1.43 (food effect).

The $AUC_{inf}$ ratio and $C_{max}$ ratio for individual subjects receiving Formulation D in the fasted and fed states is presented in Table VI. An analysis of the data indicated that 68% of the subjects receiving Formulation D had no/moderate food effect compared to 25% for Geodon capsules. In this analysis, no food effect corresponded to the pharmacokinetic ratio being between 0.80 and 1.25, a moderate food effect corresponded to the pharmacokinetic ratio being between 0.70 and 1.43, and a food effect corresponded to a ratio less than 0.70 or greater than 1.43. The fasted and fed $AUC_{inf}$ and $C_{max}$ ratios for Formulation D compared to Geodon capsules in the fed state for individual subjects is presented in Table VII. An analysis of the data showed that a majority of subjects receiving Formulation D had a fasted and fed $AUC_{inf}$ and $C_{max}$ ratio between 80% and 125%.

The variability of Formulation D *versus* Geodon capsules is shown in Table VIII. In the fed state, the % CV for $AUC_{inf}$ as well as $C_{max}$ were much lower for Formulation D (22% and 25.4%, respectively) compared to Geodon capsules (39% and 52%, respectively). It should be noted that this comparison is across two separate studies. The table also shows that Geodon capsules in the fed state have some study-to-study variability.

## Pharmacokinetic Simulations

The steady-state concentration *versus* time profiles for Geodon capsules (fed) and Formulation D (fasted and fed) are presented in Fig. 5. The ratios of the pharmacokinetic parameters are presented in Table IX. The $C_{max}$ ratios for Formulation D are somewhat lower at steady-state *versus* after single dose but still higher than Geodon in the fed state (117% and 125% in the fasted and fed state, respectively).

A comparison of the simulated steady-state concentration *versus* time profiles for Geodon and Formulation D in non-compliant, compliant, and partially compliant patients is shown in Fig. 6(a–b). For the purpose of this analysis, compliant patients are considered to be those who take their medication (both AM and PM dose) with adequate food, non-compliant patients are those who take their

**Table VIII** Comparison of the Variability of Formulation D and Geodon Capsules

| Treatment (40 mg dose) | $AUC_{inf}$ (ng*hr/mL) | $C_{max}$ (ng/mL) | 40 mg dose Treatment | $AUC_{inf}$ (ng*hr/mL) | $C_{max}$ (ng/mL) |
|---|---|---|---|---|---|
| Form D fasted | 793.3 (21.9%) | 131.9 (25.4%) | Geodon fasted | 481.4 (39%) | 53.6 (52%) |
| Form D fed | 1052.5 (22.6%) | 135.3 (22.0%) | Geodon fed | 901.5 (29%) | 87.2 (29%) |
| Geodon fed | 922.8 (25.1%) | 102.9 (30.5%) | | | |

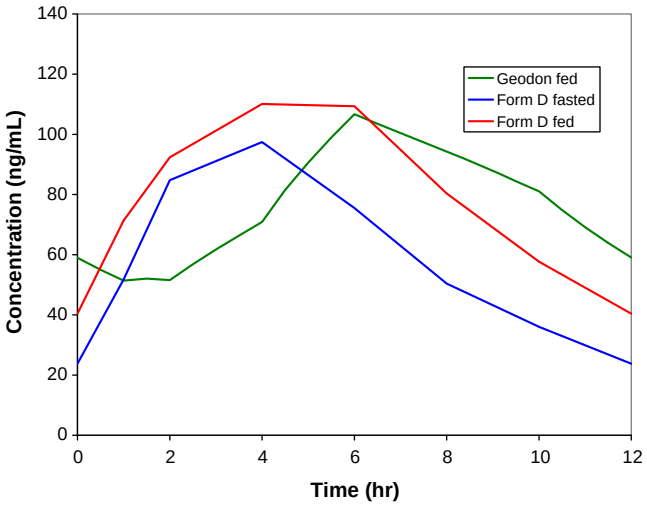


**Fig. 5** Steady-state simulations following 40 mg oral doses of Geodon® capsules in the fed state and Formulation D in the fasted and fed state.

medication in the fasted state, and partially compliant patients are those who take their AM dose in the fasted state and their PM dose in the fed state. The analysis indicated that Formulation D would be predicted to provide a more uniform response in non-compliant and partially compliant patient populations compared to Geodon capsules. On comparing Geodon and Formulation D in partially compliant patients (Fig. 6c), it is evident that Formulation D in partially compliant patients is more similar to Geodon in compliant patients than Geodon in partially compliant patients. Therefore, it would be predicted to provide a better response in partially compliant patients.

Figure 7 compares the simulated concentration *versus* time profile for an 80 mg dose of Formulation D to the profiles of 10 and 20 mg doses of IM ziprasidone taken from the literature (39). It can be seen that even at the top dose of 80 mg, the concentrations following oral administration of Formulation D are projected to be lower than those achieved on the last day of IM therapy with Geodon IM. It should be noted that the IM data is from patients, while the simulated performance of Formulation D is in healthy volunteers.

## DISCUSSION

The overall results from the pharmacokinetic studies indicated that solubilization technologies can be employed to successfully increase the extent of absorption of ziprasidone in the fasted state, thereby reducing the fed-fasted differences. However, in doing so, the rate of absorption is also increased, resulting in a higher $C_{max}$ and shorter $T_{max}$ compared to Geodon capsules administered in the fed state. Formulations which attempted to reduce the increased rate of absorption resulted in either a loss of exposure or re-introduction of the food effect, albeit not as severe as observed with Geodon capsules. Further studies would be necessary to determine the effect of meal size (calories and fat content) and meal timing. Because of the different serum concentration *versus* time profiles of the test formulations compared to Geodon capsules taken in the fed state, we discuss below safety and efficacy, primarily focusing on Formulation D, but similar considerations would apply to the other test formulations. Formulation D was selected for this detailed analysis because it exhibited a $C_{max}$ ratio relative to Geodon that was not lower than the other formulations.

### Safety Considerations

Although ziprasidone is generally well tolerated, it has a dose-related prolongation of the corrected QT (QTc) interval on ECG (40). Thus, ziprasidone is contraindicated in patients with a known history of QTc prolongation, in patients with acute myocardial infarction, and in patients with uncompensated heart failure.

Since the new formulations exhibit a higher $C_{max}$ than Geodon capsules, the improvement associated with a reduced food effect and improved variability in non-compliant patients must be balanced with possible changes in the QTc profile.

Several studies have addressed the risk-benefit profile of Geodon in the context of its QTc prolongation *versus* its neutral metabolic profile, viz., minimal effects on total and LDL cholesterol and triglyceride levels and a weight-neutral profile that distinguishes ziprasidone from other atypical antipsychotics (41). The relationship between high dose ziprasidone and QTc interval has been systematically studied, and changes from baseline QTc interval were found to be clinically modest (42). Anecdotal reports have provided preliminary indications that doses in excess of 160 mg/day and up to 640 mg/day may be safe and efficacious (43). For oral ziprasidone doses ranging from 240 to 320 mg/day, there was no significant incremental effect on QTc interval prolongation in certain subsets of

**Table IX** Simulated Steady-state Pharmacokinetic Parameters for Geodon® Capsules and Formulation D

| Treatment (40 mg dose) | $AUC_{inf}$ Ratio | $C_{max}$ Ratio |
|---|---|---|
| Formulation D (fasted) *vs* Geodon (fed) | 87% | 117% |
| Formulation D (fed) *vs* Geodon (fed) | 114% | 125% |
| Formulation D fed *vs* Formulation D fasted | 130% | 106% |

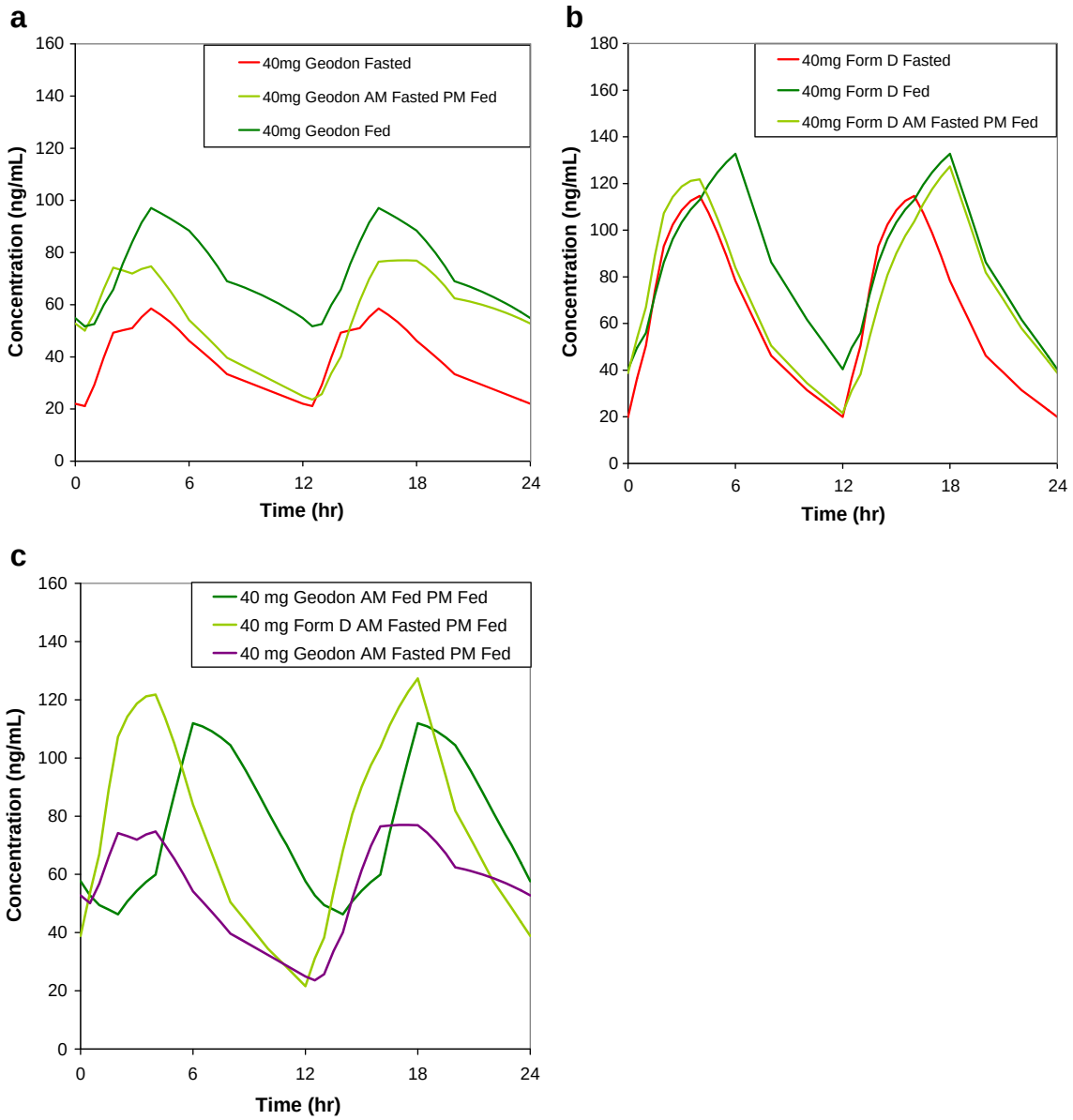


**Fig. 6** (**a**) Simulated steady-state serum ziprasidone concentrations for Geodon capsules in non-compliant, compliant, and partially compliant patients (Non-Compliant subjects = Fasted dosing; Compliant subjects = Fed dosing; Partially compliant = AM fasted and PM fed dosing). (**b**) Simulated steady-state serum ziprasidone concentrations for Formulation D in non-compliant, compliant, and partially compliant patients (Non-Compliant subjects = Fasted dosing; Compliant subjects = Fed dosing; Partially compliant = AM fasted and PM fed dosing). (**c**) Simulated steady-state serum ziprasidone concentrations comparing Geodon capsules and Formulation D in partially compliant patients (Partially compliant = AM fasted and PM fed dosing).

patients (44). Previous clinical studies, albeit with a small number of patients, have studied QTc prolongation with mean ziprasidone serum concentrations of up to 320 ng/mL, with none of the patients having a QTc interval ≥ 480 msec (42). In a retrospective review of a 14,000 patient data set, there appeared to be no evidence of a correlation between ziprasidone dosage, which ranged from 180 to 640 mg/day (mean 283.8 mg/day; SD, 71.3), and QTc interval (45). Intramuscular ziprasidone is typically used for the acute treatment of agitation in schizophrenic patients at doses of 10 mg (every 2 h) to 20 mg (every 4 h) up to a maximum of 40 mg per day. Following a typical IM regimen results in $C_{max}$ values which are typically higher than those obtained following orally dosed ziprasidone.

Based on multiple previous studies, the QTc safety of reduced food effect formulations appears to be supported given the small increase in $C_{max}$. Specifically for Formulation D, the $C_{max}$, even at the highest dose of 80 mg, is projected to be lower than the $C_{max}$ achieved in patients on Day 3

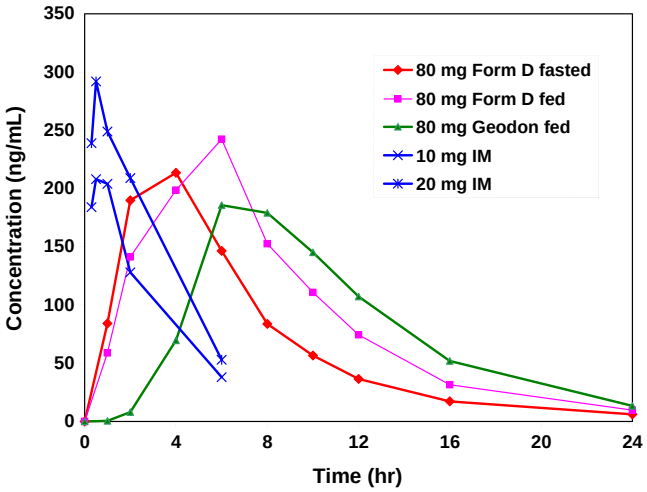


**Fig. 7** Simulated concentration *versus* time profiles for 80 mg Formulation D in the fasted and fed state compared to intramuscularly administered 10 and 20 mg Geodon.

following the last IM dose (46). We acknowledge that that ziprasidone IM is given to patients in acute need of treatment in an emergency room setting, and both the risk and risk-benefit ratio for IM dosing would be different from patients exposed to twice daily oral doses for many years. It should also be noted that the pharmacokinetic profiles are similar at steady-state for Formulation D compared to Geodon capsules with only an approximately 30% increase in $C_{max}$.

### Efficacy Considerations

For the formulations with reduced food effect, the efficacy should be similar to Geodon capsules administered in the fed state based on similar average exposures. Compared with Geodon capsules taken without a meal or taken with only a light meal (insufficient calories), the ziprasidone exposure after taking the test formulations would be higher and consequently should provide improved efficacy.

## CONCLUSIONS

Four formulations of ziprasidone utilizing advanced drug delivery technologies were developed which can be taken in either the fasted or the fed state with total exposures ($AUC_{inf}$) comparable to Geodon capsules dosed in the fed state. Two of the formulations, Formulation A, utilizing an inclusion complex with cyclodextrin as the solubilization technology, and Formulatoin D, utilizing the CSDD technology, were comparable to Geodon capsules dosed in the fed state with respect to total exposure ($AUC_{inf}$). However, the peak serum concentrations ($C_{max}$) for both these formulations in the fasted and fed state were higher than Geodon capsules dosed in the fed state, 33–50% in the case of Formulation A and about 30% higher in the case of Formulation D. Although these new formulations did not meet the FDA guidance regarding bioequivalence (both for AUC and $C_{max}$), we believe that there is significant patient and physician benefit in a no/reduced food effect ziprasidone formulation.

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## REFERENCES

1. Greenberg WM, Citrome L. Ziprasidone for schizophrenia and bipolar disorder: a review of the Clinical trials. CNS Drug Rev. 2007;13(2):137–77.
2. Patel NC, Keck Jr PE. Ziprasidone: efficacy and safety in patients with bipolar disorder. Expert Rev Neurother. 2006;6 (8):1129–38.
3. Miceli JJ, Wilner KD, Hansen RA, Johnson AC, Apseloff G, Gerber N. Single- and multiple-dose pharmacokinetics of ziprasidone under nonfasting conditions in healthy male volunteers. Br J Clin Pharmacol. 2000;49 Suppl 1:5S–13.
4. Lincoln J, Stewart Mark E, Preskorn Sheldon H. How sequential studies inform drug development: evaluating the effect of food intake on optimal bioavailability of ziprasidone. J Psychiatr Pract. 2010;16(2):103–14.
5. Miceli Jeffrey J, Glue P, Alderman J, Wilner K. The effect of food on the absorption of oral ziprasidone. Psychopharmacol Bull. 2007;40(3):58–68.
6. Gandelman K, Alderman JA, Glue P, Lombardo I, La Badie RR, Versavel M, *et al.* The impact of calories and fat content of meals on oral ziprasidone absorption: a randomized, open-label, crossover trial. J Clin Psychiat (Memphis, TN, United States). 2009;70(1):58–62.
7. Hamelin BA, Allard S, Laplante L, Miceli J, Wilner KD, Tremblay J, *et al.* The effect of timing of a standard meal on the pharmacokinetics and pharmacodynamics of the novel atypical antipsychotic agent ziprasidone. Pharmacotherapy. 1998;18(1):9–15.
8. Citrome L. Using oral ziprasidone effectively: the food effect and dose-response. Adv Ther. 2009;26(8):739–48.

9. Fagiolini A, Canas F, Gallhofer B, Larmo I, Levy P, Montes JM, *et al.* Strategies for successful clinical management of schizophrenia with ziprasidone. Expert Opin Pharmacother. 2010;11(13):2199–220.
10. Geodon [U.S. Prescribing Information including Patient Summary of Information] P, Inc., Revised Nov. 2009.
11. Perkins Diana O. Predictors of noncompliance in patients with schizophrenia. J Clin Psychiatr. 2002;63(12):1121–8.
12. Harvey PD, Bowie CR. Ziprasidone: efficacy, tolerability, and emerging data on wide-ranging effectiveness. Expert Opin Pharmacother. 2005;6(2):337–46.
13. Welling PG. Effects of food on drug absorption. Annu Rev Nutr. 1996;16:383–415.
14. Singh BN. Effects of food on clinical pharmacokinetics. Clin Pharmacokinet. 1999;37(3):213–55.
15. Stella VJ, Nti-Addae KW. Prodrug strategies to overcome poor water solubility. Adv Drug Deliv Rev. 2007;59(7):677–94.
16. Fleisher D, Bong R, Stewart BH. Improved oral drug delivery: solubility limitations overcome by the use of prodrugs. Adv Drug Deliv Rev. 1996;19(2):115–30.
17. Serajuddin ATM. Salt formation to improve drug solubility. Adv Drug Deliv Rev. 2007;59(7):603–16.
18. Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev. 2007;59(7):617–30.
19. Porter CJH, Pouton CW, Cuine JF, Charman WN. Enhancing intestinal drug solubilization using lipid-based delivery systems. Adv Drug Deliv Rev. 2008;60(6):673–91.
20. Tang J-l, Sun J, He Z-G. Self-emulsifying drug delivery systems: strategy for improving oral delivery of poorly soluble drugs. Curr Drug Ther. 2007;2(1):85–93.
21. Humberstone AJ, Charman WN. Lipid-based vehicles for the oral delivery of poorly water soluble drugs. Adv Drug Deliv Rev. 1997;25(1):103–28.
22. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. Adv Drug Deliv Rev. 2007;59(7):645–66.
23. Merisko-Liversidge E, Liversidge GG, Cooper ER. Nanosizing: a formulation approach for poorly-water-soluble compounds. Eur J Pharm Sci. 2003;18(2):113–20.
24. Kesisoglou F, Panmai S, Wu Y. Nanosizing—Oral formulation development and biopharmaceutical evaluation. Adv Drug Deliv Rev. 2007;59(7):631–44.
25. Friesen DT, Shanker R, Crew M, Smithey DT, Curatolo WJ, Nightingale JAS. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview. Mol Pharm. 2008;5(6):1003–19.
26. Shah JC. Novel injectable depot formulations of heterocyclic aryl compounds. Application: WO. WO patent 2003-IB4576 2004037289. 2004 20031013
27. Shah JC, Shah PS, Wisniecki P, Wagner DR. Injectable depot formulations and methods for providing sustained release of nanoparticle compositions. Application: US. US patent 2008–43014 2008305161. 2008 20080305
28. Babcock WC, Caldwell WB, Crew MD, Friesen DT, Smithey DT, Shanker RM. Pharmaceutical compositions of semi-ordered drugs and polymers. Application: WO.WO patent 2003-IB3465 2004014342. 2004 20030731.
29. Janiszewski JS, Fouda HG, Cole RO. Development and validation of a high-sensitivity assay for an antipsychotic agent, CP-88,059, with solid-phase extraction and narrow-bore high-performance liquid chromatography. J Chromatogr B Biomed Appl. 1995;668(1):133–9.
30. Phase I Study to Access the Safety, Toleration, and Pharmacokinetics of CP-88,059-1 Following Escalating Single Oral Doses under Fasting and Non-fasting conditions in Normal Healthy Male Volunteers, Pfizer Inc. 1996
31. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry; Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations, March, 2003
32. Boddy AW, Snikeris FC, Kringle RO, Wei GCG, Oppermann JA, Midha KK. An approach for widening the bioequivalence acceptance limits in the case of highly variable drugs. Pharm Res. 1995;12(12):1865–8.
33. Diletti E, Hauschke D, Steinijans VW. Sample size determination: extended tables for the multiplicative model and bioequivalence ranges of 0.9 to 1.11 and 0.7 to 1.43. Int J Clin Pharmacol Ther Toxicol. 1992;30 Suppl 1:S59–62.
34. Hauck WW, Parekh A, Lesko LJ, Chen ML, Williams RL. Limits of 80%–125% for AUC and 70%–143% for Cmax. What is the impact on bioequivalence studies? Int J Clin Pharmacol Ther. 2001;39(8):350–5.
35. Karalis V, Macheras P, Symillides M. Geometric mean ratio-dependent scaled bioequivalence limits with leveling-off properties. Eur J Pharm Sci. 2005;26(1):54–61.
36. Kytariolos J, Karalis V, Macheras P, Symillides M. Novel scaled bioequivalence limits with leveling-off properties. Pharm Res. 2006;23(11):2657–64.
37. Tothfalusi L, Endrenyi L, Midha KK. Scaling or wider bioequivalence limits for highly variable drugs and for the special case of Cmax. Int J Clin Pharmacol Ther. 2003;41(5):217–25.
38. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. DRAFT Guidance for Food Effect Bioavailability and Bioequivalence Studies (December, 1997)
39. Miceli J, Preskorn S, Wilner K, Folger C, Tensfeldt T. Characetrization of the intramuscular pharmacokinetics of ziprasidone in schizophrenic patients. Eur Psychiatry. 1998;13 suppl 4:304S–5.
40. Taylor D. Ziprasidone in the management of schizophrenia: the QT interval issue in context. CNS Drugs. 2003;17(6):423–30.
41. Daniel DG. Tolerability of ziprasidone: an expanding perspective. J Clin Psychiatry. 2003;64 Suppl 19:40–9.
42. Miceli JJ, Tensfeldt TG, Shiovitz T, Anziano RJ, O'Gorman C, Harrigan RH. Effects of high-dose ziprasidone and haloperidol on the QTc interval after intramuscular administration: a randomized, single-blind, parallel-group study in patients with schizophrenia or schizoaffective disorder. Clin Ther. 2010;32(3):472–91.
43. Citrome L, Jaffe A, Levine J. How dosing of ziprasidone in a state hospital system differs from product labeling. J Clin Psychiat (Memphis, TN, United States). 2009;70(7):975–82.
44. Levy Woodburne O, Robichaux-Keene Nicole R, Nunez C. No significant QTc interval changes with high-dose ziprasidone: a case series. J Psychiatr Pract. 2004;10(4):227–32.
45. Deutschman Daniel A, Deutschman Douglas H. High-dose ziprasidone in treatment-resistant schizophrenia and affective spectrum disorders: a case series. J Clin Psychopharmacol. 2007;27(5):513–4.
46. Miceli JJ, Wilner KD, Swan SK, Tensfeldt TG. Pharmacokinetics, safety, and tolerability of intramuscular Ziprasidone in healthy volunteers. J Clin Pharmacol. 2005;45(6):620–30.