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# Bioequivalence of Ondansetron Oral Soluble Film 8 mg (ZUPLENZ) and Ondansetron Orally Disintegrating Tablets 8 mg (ZOFRAN) in Healthy Adults

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Oral formulations of ondansetron are used to prevent nausea and vomiting associated with chemotherapy, radiotherapy, and surgery. An oral soluble film formulation of ondansetron (OND OSF) was developed using MonoSol Rx's proprietary PharmFilm technology and was formulated to dissolve rapidly on the tongue, without the need for water. This product provides an oral antiemetic treatment option for patients who experience difficulty swallowing. The purpose of this study was to compare the bioequivalence of OND OSF 8 mg (ZUPLENZ, Monosol Rx, Warren, NJ) with ondansetron orally disintegrating tablets (OND ODT) 8 mg (ZOFRAN, GlaxoSmithKline, Research Triangle Park). In 3 individual open-label, randomized studies, healthy adult subjects received a single dose of OND OSF 8 mg and a single dose of OND ODT 8 mg, under fasted conditions (study 1, n = 48), fed conditions (study 2, n = 48), and fasted with and without water (study 3, n = 18). Each dosing period was followed by a 3- or 7-day washout period. Ondansetron pharmacokinetics were assessed predose to 24 hours postdose for the single 8-mg doses of OND OSF and OND ODT. All analyses were conducted on natural log-transformed pharmacokinetic parameters for OND OSF and OND ODT. Under both fasted and fed conditions, the 90% confidence interval for the comparisons of OND OSF and OND ODT plasma ondansetron area under the curve from time 0 to the last measured concentration ($AUC_{0-t}$), area under the concentration vs. time curve from time 0 to infinity ($AUC_{0-\infty}$), and maximum plasma concentration ($C_{max}$) were within the 80%–125% range, indicating bioequivalence between the formulations. With features designed to make it portable and easy to take, OND OSF 8 mg provides an alternative treatment option, particularly for patients with dysphagia and others who find it difficult to take oral tablets.

*Keywords:* ondansetron, oral soluble film, bioequivalence, nausea, vomiting

## INTRODUCTION

Ondansetron is a selective 5-$HT_3$ receptor antagonist indicated for the prevention of chemotherapy-induced, radiotherapy-induced, and postoperative nausea and vomiting.[1–3] If untreated, nausea and vomiting can have serious consequences, including nutritional depletion, anorexia, and deterioration of patients' physical and mental status, as well as increased health care costs.[3,4] Oral formulations of ondansetron[5] are known to prevent nausea and vomiting in patients after surgery and in those receiving cancer chemotherapy or radiotherapy.[6–9] However, some patients are known to have difficulty ingesting tablets, especially during periods of nausea and vomiting. Similarly, there are patients who have other medical conditions that make swallowing tablets challenging, such as those who experience dysphagia or xerostomia (dry mouth) as a result of chemotherapy and radiation.[11,12]

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Therefore, from a clinical perspective, there is a need for an easy-to-take oral formulation that dissolves rapidly in the mouth, can be taken with or without water, and can be dosed before or after surgery, chemotherapy, or radiotherapy. Advances in drug delivery systems have led to the development of an oral soluble film (OSF) formulation using a proprietary technology that provides a dissolvable polymer matrix for drug delivery—PharmFilm (MonoSol Rx, Warren, NJ). On application to the tongue, the OSF rapidly dissolves, quickly releasing the active drug substance. One such formulation is ondansetron (OND) OSF 8 mg, a quickly dissolving film that is placed on the tongue.[1] An oral soluble film formulation of ondansetron (OND OSF) 8 mg is portable, can be administered anytime, anywhere, with or without water, and provides an appropriate treatment option for patients who experience difficulty swallowing tablets or those who object to other forms of ondansetron administration.

Three randomized, clinical studies evaluated the bioequivalence of OND OSF 8 mg (ZUPLENZ, Monosol Rx, Warren, NJ) and ondansetron orally disintegrating tablets (OND ODT) 8 mg (ZOFRAN; GlaxoSmithKline, Research Triangle Park, NC), taken with or without water, and under fasted and fed conditions, in healthy adult subjects. The relative safety and tolerance of the study drug formations under both fasted and fed conditions were also assessed.

# MATERIALS AND METHODS

## Materials

*Ondansetron OSF*

Ondansetron OSF is manufactured using a wet-casting method in which the drug is suspended in an aqueous mixture of film-forming polymers, flavors, sweeteners, buffering salts, plasticizers, opacifiers, and a preservative. The viscous mixture is then coated onto an inert mylar substrate to a predetermined thickness using a direct reverse roll-coating technique. The coated mylar is passed through horizontal ovens and dried to a specific moisture content using perpendicular airflow. After drying, the bulk film roll is sufficiently self-supporting to allow removal of the mylar substrate. The mylar substrate is removed and the bulk film roll is cut into individual ribbons of a known width. Each ribbon is then cut into individual dosage units of known length based on the concentration of ondansetron per unit area of film. Finally, each dosage unit is packaged between 2 layers of foil composite and heat sealed at the edges to form a sachet.

*Ondansetron orally disintegrating tablets 8 mg*

The 8-mg OND ODT were purchased from a commercial supplier, stored as recommended by the manufacturer, and used as is.

## Study design

Three open-label, randomized, single-dose, crossover studies were conducted at the Vimta VHS Research Centre in Adyar, Chennai, India. In each study, healthy adult subjects received single doses of OND OSF 8 mg and OND ODT 8 mg during alternating treatment periods according to randomly assigned sequences. In study 1, subjects were administered OND OSF 8 mg and OND ODT 8 mg under fasted conditions; in study 2, subjects were administered OND OSF 8 mg and OND ODT 8 mg under fed conditions; in study 3, subjects were administered OND OSF 8 mg with and without water and OND ODT 8 mg without water under fasted conditions.

The studies were carried out in accordance with the Declaration of Helsinki, the International Conference on Harmonisation-Good Clinical Practice, the Central Drugs Standard Control Organization Schedule Y, and the Indian Council of Medical Research Ethical Guidelines for Biomedical Research on Human Study Participants. The protocol and informed consent form were reviewed and approved by the institutional review board (Independent Ethics Committee, Chennai, India), and all subjects provided written informed consent before participating.

## Subjects

Healthy men and women aged 18–45 years with a body mass index between 18.5 and 25 kg/m$^2$, a body weight of $\geq$50 kg, systolic blood pressure between $\geq$90 and $\leq$140 mm Hg, diastolic blood pressure between $\geq$60 and $\leq$90 mm Hg, and determined to be in good health by medical history and physical examination, including electrocardiogram, chest x-ray, and vital signs, were eligible to participate. Women of childbearing potential were required to practice abstinence or use an acceptable method of birth control for the duration of the study. Exclusion criteria included[1] the inability to understand informed consent[2]; a history of hypersensitivity or idiosyncratic reaction to the study drug or to other related drugs[3]; evidence of impaired renal, hepatic, cardiac, lung, or gastrointestinal function[4]; smoking, or the use of any over-the-counter or prescribed medication including enzyme-modifying drugs or any systemic medication within the past 30 days[5]; a history of psychiatric illness that may interfere with full participation in the study[6]; a history of alcohol or substance abuse within the last 5 years; or[7] clinically



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significant abnormal laboratory values. In addition, subjects were ineligible[1] if the study drug was contraindicated for medical reasons,[2] if they had participated in any other clinical investigation of an experimental drug or had bled ≥350 mL in the past 3 months,[3] if they were intolerant to venipuncture, or[4] if they were unlikely to be compliant with protocol requirements. Female subjects were also excluded if they used implanted or injected hormonal contraceptives during the past 6 months or oral hormonal contraceptives in the past 14 days, were pregnant, or breastfeeding.

**Treatment**

*Studies 1 and 2*

Studies 1 and 2 were 2-period, 2-way crossover studies during which the study drugs were administered according to 1 of 2 treatment sequences (AB or BA), based on a randomization schedule. Subjects received a single dose of OND OSF 8 mg (A) and OND ODT 8 mg (B), and each treatment period was separated by a 7-day washout period. All doses were orally administered, allowed to dissolve, swallowed with saliva, and followed by 240 mL of room temperature water. Subjects were confined to the study center from at least 12 hours before dosing through 24 hours postdose. Those subjects treated under fasted conditions underwent a ≥10-hour fast overnight before drug administration and continued to fast for 4 hours postdose. Subjects treated under fed conditions underwent a ≥10-hour fast overnight followed by a standard high-fat breakfast that was served 30 minutes before drug administration.

*Study 3*

Study 3 was a 3-period, 3-way crossover study during which study drugs were administered according to 1 of 3 treatment sequences (ABC, BCA, and CAB), based on a randomization schedule. Subjects received a single dose of OND OSF 8 mg administered without water (A), a single dose of OND OSF 8 mg administered with water (B), and a single dose of OND ODT 8 mg administered without water (C). Each treatment period was separated by a 3-day washout period. Subjects were confined to the study center from at least 12 hours before dosing through 24 hours postdose. Treatments were administered after an overnight fasting period of ≥10 hours in each of the 3 treatment periods.

**Assessments**

*Pharmacokinetics*

During each treatment period, blood samples for pharmacokinetic analysis were collected within 1 hour before drug administration (0 hours) and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 4, 6, 8, 10, 12, 15, 18, and 24 hours after drug administration. Blood samples collected during the first 10 hours postdose were obtained from an indwelling intravenous cannula, whereas the remaining blood samples were collected by means of fresh, clean, sterile venipuncture. After collection, the blood samples were placed in a thermocol box containing ice packs or similar cooling device. Within 30 minutes after collection, blood samples were centrifuged at 3800 rpm for 10 minutes at 10°C ± 2°C. The plasma from each sample was then pipetted into 2 sets in polypropylene tubes and immediately stored at −16°C or colder pending analysis. Plasma samples ready for analysis were sent to the bioanalytical facility (Vimta, Hyderabad) under frozen conditions.

The ondansetron concentration of each plasma sample was determined using a validated HPLC-MS/MS assay developed at Vimta Labs Limited and performed under ultraviolet filtered lighting conditions. Pharmacokinetic parameters [area under the concentration vs. time curve from time 0 to infinity ($AUC_{0-\infty}$), AUC from time 0 to the last measured concentration ($AUC_{0-t}$), maximum plasma concentration ($C_{max}$), time to $C_{max}$ ($t_{max}$)], and the apparent first-order elimination or terminal rate constant were calculated from the plasma concentration data using a noncompartmental model for ondansetron (WinNonlin Ent-Version 4.1; Pharsight Corporation, St. Louis, MO). $AUC_{0-t}$ was calculated using the linear trapezoid rule, and $AUC_{0-\infty}$ was calculated as the sum of the $AUC_{0-t}$ plus the ratio of the last measured plasma concentration to the elimination rate constant. The elimination rate constant ($k_{el}$) was calculated by linear least-square regression analysis using the last 3 or more nonzero plasma concentration of the terminal phase. The terminal half-life ($t_{1/2}$) was calculated as $0.693/k_{el}$.

*Safety*

To ensure the safety of the subject, safety assessments including the monitoring of adverse events (AEs) and adverse drug reactions, periodic physical examination, and vital signs monitoring at regular predetermined intervals were conducted throughout the study. Before the start of the study, a 12-lead electrocardiogram, chest x-ray, urinalysis, and serology were conducted to screen volunteers. In addition, hematology and serum chemistry assessments were performed to select study participants with baseline values within reference ranges. After study, the subjects were screened again to determine whether any clinically significant abnormalities were present. Urine drug screening was done at the time of check-in for all study periods to confirm the lack of any



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substance abuse. Urine pregnancy screen (for female volunteers) was performed at the time of check-in of all study periods and at study conclusion. A clinical assessment, which included medical history and a general and systemic examination, was completed during the prestudy screening and again at poststudy examination.

*Statistical analyses*

The pharmacokinetic population comprised all subjects who received OND OSF 8 mg and OND ODT 8 mg and completed the study. Pharmacokinetic parameters were measured for all subjects determined to have sufficient plasma concentration data to enable the calculation of $C_{max}$ and AUC. Statistical analyses were performed on all pharmacokinetic data, and all analyses were conducted using logarithmically (natural) transformed parameters generated by SAS 9.1.3 Enterprise Guide Version 3.0 (SAS Institute Inc., Cary, NC).

In addition, descriptive statistics such as n, mean, SD, minimum, maximum, median, and coefficient of variation were calculated for all pharmacokinetic parameters. The geometric mean was calculated for $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$. For $t_{max}$, the median was reported as descriptive statistics. The linear mixed effect model was used to assess the relative bioavailability of OND OSF 8 mg and OND ODT 8 mg. The pharmacokinetic parameters $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ were natural log transformed before analysis. The model included terms for sequence, period, and treatment as fixed effects and study participants nested within sequence as random effect. Within the framework of mixed-effects model, the least squares means for OND OSF 8 mg and OND ODT 8 mg, the difference between the least squares means of OND OSF 8 mg versus OND ODT 8 mg, and the corresponding 90% confidence intervals (CIs) for the difference between the least squares means were calculated in natural log scale. The least squares means, the least squares mean differences, the 90% CIs obtained in the natural log scale, the ratio estimates, and the 90% CI of ratio estimates in the original scale were calculated. If the 90% CIs of the ratio estimates of $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ for ondansetron were all within the 80%–125% range, it was concluded that the OND OSF 8 mg was bioequivalent to the OND ODT 8 mg.

The safety population was composed of all subjects who received more than 1 dose of OND OSF 8 mg or OND ODT 8 mg, and the safety variables were summarized descriptively by treatment.

## RESULTS

A total of 114 subjects (91 men and 23 women) were enrolled across the 3 studies, and the subject disposition is summarized in Table 1. In studies 1, 2, and 3, there were 48, 48, and 18 subjects enrolled, respectively, with 46, 45, and 17 subjects completing the clinical phase, respectively. In study 1, 2 subjects discontinued the study for personal reasons other than an AE. In study 2, 3 subjects were discontinued due to positive urine screen for substance abuse (n = 1), personal reasons other than an AE (n = 1), and noncompliance in consumption of a high-fat breakfast (n = 1). In study 3, 1 subject was discontinued due to a positive urine screen for substance abuse. All plasma ondansetron concentrations and pharmacokinetic parameters were based on data from subjects who completed all 3 study periods.

The demographics and baseline characteristics of the subjects in the pharmacokinetic population were similar in the 3 studies (Table 2). Across the 3 studies, the

**Table 1.** Subject dispositions.

| Disposition | Study 1, fasted (n) | Study 2, fed (n) | Study 3, fasted water effect (n) |
|---|---|---|---|
| Subjects randomized and enrolled | 48 | 48 | 18 |
| Subjects in safety analysis | 48 | 48 | 18 |
| Subjects who completed the study | 46 | 45 | 17 |
| Subjects who discontinued the study | 2 | 3 | 1 |
| Main reason for discontinuation from study | | | |
| Personal reasons other than an AE | 2 | 1 | — |
| Noncompliance | — | 1 | — |
| Positive urine screen for substance abuse | — | 1 | 1 |
| Subjects in pharmacokinetic analysis | 46 | 45 | 17 |



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**Table 2.** Demographic and baseline characteristics (pharmacokinetic population).

| Parameter | Study 1, fasted (n = 46) | Study 2, fed (n = 45) | Study 3, fasted water effect (n = 17) |
|---|---|---|---|
| Age, yrs | | | |
| Mean ± SD | 26.4 ± 5.7 | 26.8 ± 5.8 | 28.2 ± 6.6 |
| Median | 24 | 26 | 26 |
| Min–Max | 18–40 | 18–41 | 19–39 |
| CV | 21.6 | 21.6 | 23.4 |
| Weight, kg | | | |
| Mean ± SD | 61.2 ± 7.3 | 59.2 ± 7.0 | 64.5 ± 9.3 |
| Median | 61 | 58 | 66 |
| Min–Max | 50–80 | 50–73 | 50–84 |
| CV | 11.9 | 11.8 | 14.4 |
| Height, cm | | | |
| Mean ± SD | 166.1 ± 8.4 | 163.9 ± 9.1 | 161.0 ± 13.9 |
| Median | 167 | 165 | 166 |
| Min–Max | 148–182 | 146–178 | 124–180 |
| CV | 5.0 | 5.5 | 8.6 |
| BMI, kg/m$^2$ | | | |
| Mean ± SD | 22.1 ± 2.1 | 22.1 ± 2.4 | 23.7 ± 1.4 |
| Median | 22 | 23 | 24 |
| Min–Max | 19–25 | 19–25 | 19–25 |
| CV | 9.6 | 10.9 | 6.0 |

BMI, body mass index; CV, coefficient of variation.

mean age was 26–28 years and the mean body mass index was 22–24 kg/m$^2$.

### Plasma ondansetron pharmacokinetics

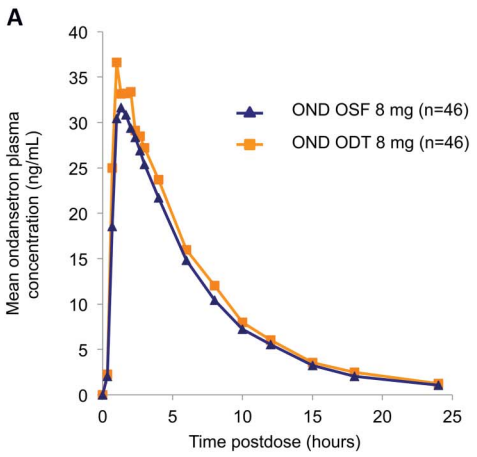
The mean plasma ondansetron concentration versus time profile of OND OSF 8 mg was similar to that of OND ODT 8 mg under fasted conditions, when taken with food, and when taken with or without water (Figure 1). Each profile exhibited a maximum ondansetron concentration at approximately 1–3 hours postdose, followed by a gradual decline over the next 21 hours. Systemic plasma ondansetron exposure (AUC and $C_{max}$) was also similar after single doses of OND OSF 8 mg and OND ODT 8 mg (Figure 1). The mean ondansetron $AUC_{0-t}$ values for OND OSF 8 mg and OND ODT 8 mg, respectively, were 216.27 ± 83.29 and 239.46 ± 100.07 $ng \cdot h^{-1} \cdot mL^{-1}$ when administered under fasted conditions, 201.02 ± 92.66 and 212.12 ± 96.45 $ng \cdot h^{-1} \cdot mL^{-1}$ when administered after a high-fat breakfast, and 290.69 ± 106.52 and 285.46 ± 105.30 $ng \cdot h^{-1} \cdot mL^{-1}$ when administered under fasted conditions without water. The mean ondansetron $C_{max}$ values for OND OSF 8 mg and OND ODT 8 mg were similar under all dosing conditions (Figure 1). In addition, the $t_{max}$ values were similar for the 2 formulations in each of the 3 studies. The median ondansetron $t_{max}$ values for OND OSF 8 mg and OND ODT 8 mg were 1.33 (1.00–4.00) and 1.17 (0.67–3.00) hours, respectively, when administered under fasted conditions, 2.67 (1.00–4.00) and 2.67 (0.67–6.00) hours when administered after a high-fat breakfast, and 2.00 (1.00–2.67) and 1.67 (1.67–3.00) hours when administered under fasted conditions without water.

### Bioequivalence

The rate and extent of ondansetron absorption parameters ($C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$) for OND OSF 8 mg and OND ODT 8 mg were found to be similar (Table 3). The 90% CIs of the ratios of OND OSF 8 mg versus OND ODT 8 mg for the absorption parameters $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ were 85.46–97.10 ng/mL, 88.26–96.42 $ng \cdot h^{-1} \cdot mL^{-1}$, and 87.74–95.88 $ng \cdot h^{-1} \cdot mL^{-1}$, respectively, when administered under fasted conditions; 94.68–106.00 ng/mL, 88.97–98.40 $ng \cdot h^{-1} \cdot mL^{-1}$, and 89.15–98.63 $ng \cdot h^{-1} \cdot mL^{-1}$, respectively, when administered after a high-fat breakfast; and 93.57–114.21 ng/mL, 96.50–108.51 $ng \cdot h^{-1} \cdot mL^{-1}$, and 96.31–108.82 $ng \cdot h^{-1} \cdot mL^{-1}$, respectively, when administered under fasted conditions without water. Overall, the 90% CIs for the comparisons of OND OSF and OND ODT plasma ondansetron $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ were all within the

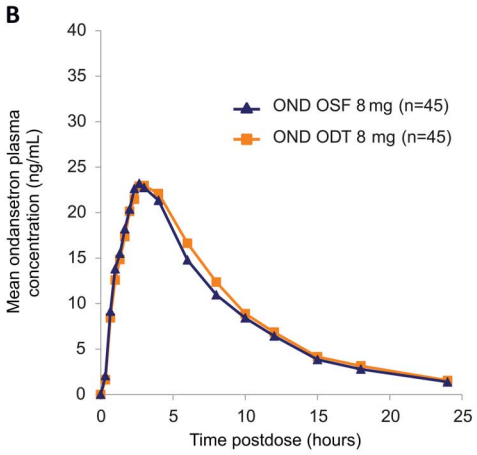


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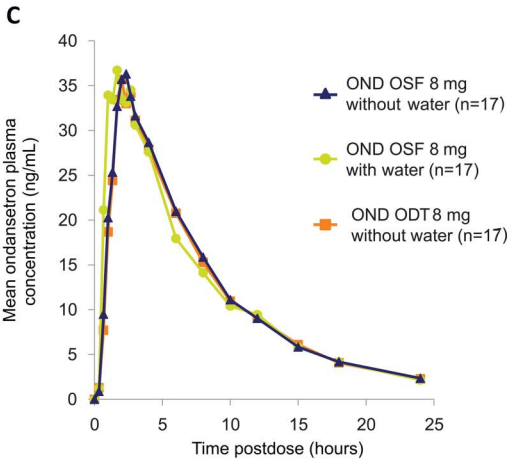

Study 1, fasted (n=46)

| Pharmacokinetic parameter | OND OSF 8 mg | OND ODT 8 mg |
|---|---|---|
| $C_{max}$ (ng/mL); mean ± SD | 37.28 ± 14.92 | 41.11 ± 17.24 |
| $AUC_{0-t}$ (ng•h/mL); mean ± SD | 216.27 ± 83.29 | 239.46 ± 100.07 |
| $AUC_{0-\infty}$ (ng•h/mL); mean ± SD | 225.03 ± 88.26 | 250.67 ± 107.97 |
| $T_{max}$ (h); median (min-max) | 1.33 (1.00-4.00) | 1.17 (0.67-3.00) |
| $t_{1/2}$ (h); mean ± SD | 4.67 ± 0.85 | 4.79 ± 1.17 |
| $K_{el}$ ($h^{-1}$); mean ± SD | 0.154 ± 0.04 | 0.156 ± 0.06 |




Study 2, fed (n=45)

| Pharmacokinetic parameter | OND OSF 8 mg | OND ODT 8 mg |
|---|---|---|
| $C_{max}$ (ng/mL); mean ± SD | 26.02 ± 9.53 | 25.69 ± 8.69 |
| $AUC_{0-t}$ (ng•h/mL); mean ± SD | 201.02 ± 92.66 | 212.12 ± 96.45 |
| $AUC_{0-\infty}$ (ng•h/mL); mean ± SD | 213.71 ± 102.27 | 225.89 ± 110.87 |
| $T_{max}$ (h); median (min-max) | 2.67 (1.00-4.02) | 2.67 (0.67-6.00) |
| $t_{1/2}$ (h); mean ± SD | 5.09 ± 0.98 | 5.15 ± 0.99 |
| $K_{el}$ ($h^{-1}$); mean ± SD | 0.142 ± 0.03 | 0.139 ± 0.03 |




Study 3, fasted water effect (n=17)

| Pharmacokinetic parameter | OND OSF 8 mg (without water) | OND OSF 8 mg (followed by water) | OND ODT 8 mg (without water) |
|---|---|---|---|
| $C_{max}$ (ng/mL); mean ± SD | 40.87 ± 13.31 | 42.84 ± 15.91 | 39.38 ± 12.36 |
| $AUC_{0-t}$ (ng•h/mL); mean ± SD | 290.69 ± 106.52 | 291.07 ± 99.59 | 285.46 ± 105.30 |
| $AUC_{0-\infty}$ (ng•h/mL); mean ± SD | 311.35 ± 119.79 | 310.39 ± 112.75 | 306.50 ± 121.83 |
| $T_{max}$ (h); median (min-max) | 2.00 (1.00-2.67) | 1.67 (0.67-3.00) | 1.67 (1.67-3.00) |
| $t_{1/2}$ (h); mean ± SD | 5.57 ± 1.09 | 5.74 ± 0.92 | 5.46 ± 1.38 |
| $K_{el}$ ($h^{-1}$); mean ± SD | 0.129 ± 0.24 | 0.124 ± 0.02 | 0.135 ± 0.04 |

**FIGURE 1.** Mean ondansetron plasma concentrations 0–24 hours after single doses of OND OSF 8 mg and OND ODT 8 mg, (A) administered under fasted conditions, (B) administered after a high-fat breakfast, and (C) administered under fasted conditions with and without water.

80%–125% range, fulfilling the criterion for bioequivalence.

In addition, both modes of administration of OND OSF 8 mg (with and without water) were bioequivalent. The 90% CIs of the ratios of OND OSF 8 mg administered without water versus OND OSF 8 mg administered with water for the absorption parameters $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ were 88.03–107.46,



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**Table 3.** Bioequivalence results: systemic plasma ondansetron exposure.

| Pharmacokinetic parameter | Least squares geometric means | | Ratio (%) | 90% CI |
|---|---|---|---|---|
| Study 1, fasted (n = 46) | OND OSF 8 mg fasted | OND ODT 8 mg fasted | | |
| $C_{max}$, ng/mL | 34.57 | 37.95 | 91.09 | 85.46–97.10 |
| $AUC_{0-t}$, $ng \cdot h^{-1} \cdot mL^{-1}$) | 201.33 | 218.24 | 92.25 | 88.26–96.42 |
| $AUC_{0-\infty}$, $ng \cdot h^{-1} \cdot mL^{-1}$) | 209.03 | 227.89 | 91.72 | 87.74–95.88 |
| Study 2, fed (n = 45) | OND OSF 8 mg fed | OND ODT 8 mg fed | | |
| $C_{max}$, ng/mL | 24.44 | 24.39 | 100.18 | 94.68–106.00 |
| $AUC_{0-t}$, $ng \cdot h^{-1} \cdot mL^{-1}$ | 182.50 | 195.05 | 93.57 | 88.97–98.40 |
| $AUC_{0-\infty}$, $ng \cdot h^{-1} \cdot mL^{-1}$) | 193.10 | 205.94 | 93.77 | 89.15–98.63 |
| Study 3, fasted water effect (n = 17) | OND OSF 8 mg without water | OND ODT 8 mg without water | | |
| $C_{max}$, ng/mL | 39.05 | 37.78 | 103.38 | 93.57–114.21 |
| $AUC_{0-t}$, $ng \cdot h^{-1} \cdot mL^{-1}$ | 275.78 | 269.51 | 102.33 | 96.50–108.51 |
| $AUC_{0-\infty}$, $ng \cdot h^{-1} \cdot mL^{-1}$ | 293.73 | 286.92 | 102.38 | 96.31–108.82 |
| | OND OSF 8 mg with water | OND ODT 8 mg without water | | |
| $C_{max}$, ng/mL | 40.152 | 37.78 | 106.28 | 96.20–117.43 |
| $AUC_{0-t}$, $ng \cdot h^{-1} \cdot mL^{-1}$ | 276.06 | 269.51 | 102.43 | 96.60–108.62 |
| $AUC_{0-\infty}$, $ng \cdot h^{-1} \cdot mL^{-1}$ | 292.46 | 286.92 | 101.93 | 95.90–108.35 |
| | OND OSF 8 mg without water | OND OSF 8 mg with water | | |
| $C_{max}$, ng/mL | 39.05 | 40.15 | 97.26 | 88.03–107.46 |
| $AUC_{0-t}$, $ng \cdot h^{-1} \cdot mL^{-1}$ | 275.78 | 276.06 | 99.90 | 94.21–105.93 |
| $AUC_{0-\infty}$, $ng \cdot h^{-1} \cdot mL^{-1}$ | 293.73 | 292.46 | 100.44 | 94.49–106.76 |

94.21–105.93, and 94.49–106.76, respectively, all within the 80%–125% range.

### Safety

In these crossover studies, safety profiles of OND OSF 8 mg and OND ODT 8 mg were similar, and both dosage forms were tolerated. In study 1, a total of 15 AEs were reported in 27% (n = 13/48) of subjects administered both OND OSF 8 mg and OND ODT 8 mg under fasted conditions. Three AEs were reported during subject confinement to the study center and included abdominal pain (n = 2) and vomiting (n = 1), all were considered mild in severity and unrelated (n = 1) or unlikely related (n = 2) to the study drug. Of the remaining AEs, 11 were cases of abnormal clinical laboratory values observed during the postclinical assessment, including increased eosinophil count (n = 2), increased aspartate transferase (n = 1), increased alanine transferase (ALT) (n = 4), increased total bilirubin (n = 1), decreased platelet count (n = 1), increased lymphocyte count (n = 1), and increased white blood cell (WBC) count in 1 subject who also reported a respiratory tract infection. All laboratory changes were considered mild in severity and resolved with no sequelae, except a single subject with a respiratory tract infection and increased WBC count was lost to follow-up.

In study 2, a total of 9 AEs were reported in 17% (n = 8/48) of subjects administered both OND OSF 8 mg and OND ODT 8 mg under fed conditions. All AEs were abnormal clinical laboratory values observed during the postclinical assessment, including increased ALT (n = 2), increased eosinophil count (n = 4), increased lymphocyte count (n = 2), and increased WBC count (n = 1). The laboratory changes were mild in severity, except for 2 cases of moderately increased eosinophil count, and all resolved with no sequelae.

In study 3, a total of 5 AEs were reported in 22% (n = 4/18) of subjects administered both OND OSF 8 mg and OND ODT 8 mg under fasted conditions, with and without water. All AEs were abnormal clinical laboratory values observed during the postclinical assessment, including increased ALT (n = 3), increased aspartate transferase (n = 1), and increased WBC count (n = 1). The laboratory changes were considered mild and resolved with no sequelae (2 subjects were lost to follow-up).

Across the 3 studies, there were no serious AEs, no significant AEs, and no deaths. There were no clinically significant changes in physical examination findings, vital signs, or laboratory findings that were deemed to be related to study drugs.



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## DISCUSSION

Three randomized clinical trials evaluated the bioequivalence of OND OSF 8 mg and OND ODT 8 mg in healthy adult subjects under fasted, with and without water, and fed conditions. Both OND OSF 8 mg and OND ODT 8 mg demonstrated overall similar plasma ondansetron concentrations postdose. The criterion for bioequivalence of plasma ondansetron exposure was met for all parameters ($AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$). Across the 3 studies, both formulations were generally well tolerated, with no discernable differences between the formulations. Based on this bioequivalence, it is expected that the OND OSF 8 mg will exhibit a clinical efficacy and safety profile similar to that of OND ODT 8 mg.

The bioequivalence findings indicate a 1:1 correspondence between doses of OND OSF 8 mg and OND ODT 8 mg with no important differences in the type or frequency of AEs events, regardless of condition of administration (fasted or fed). There was also no indication of new AEs or an increase in the frequency of AEs with OND OSF 8 mg versus OND ODT 8 mg. The bioequivalence findings of the studies reported here indicate that OND OSF 8 mg is equivalent to OND ODT 8 mg.

In conclusion, the pharmacokinetic results of these 3 studies demonstrated that a single dose of OND OSF 8 mg, taken with or without water, and under fasted or fed conditions, was bioequivalent to OND ODT 8 mg. The treatments had a similar safety profile and were generally well tolerated. OND OSF 8 mg is designed to be portable and easy for patients to take, dissolves on the tongue in 4–20 seconds,[1] and provides a treatment option for patients with dysphagia and others who find it difficult to swallow oral tablets.

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