

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209512Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA	209, 512
Type	Non-NME original NDA for the approval of new formulation
Drug	NORVIR (ritonavir)
Dosage form and strength	Powder for oral suspension, 100 mg per packet
Sponsor	Abbvie
Receipt Date	12/7/2016
PDUFA goal date	6/7/2017
Review category	Priority
Indication	Treatment of HIV infection
Clinical pharmacology reviewer	Su-Young Choi, Pharm.D., Ph.D
Clinical pharmacology team leader	Shirley Seo, Ph.D

Executive Summary

The applicant submitted a New Drug Application seeking the approval of a new formulation of NORVIR (ritonavir), powder for oral suspension. The approved indication of NORVIR is for the treatment of HIV-1 infection (600 mg BID) but it is no longer used as an antiretroviral agent. Instead, it is used as a CYP3A inhibitor at lower doses (200 mg and lower) to increase the exposure of antiretroviral drugs that are CYP3A substrates (i.e., protease inhibitors). The currently approved NORVIR formulation for pediatric use is an oral solution containing ethanol and propylene glycol. Due to safety concerns over these excipients, AbbVie has developed an alternate formulation of ritonavir which does not contain ethanol or propylene glycol.

To support the approval of NORVIR powder for oral suspension, the pivotal BA/BE trial was conducted to compare the pharmacokinetics of ritonavir using the NORVIR powder for oral suspension and the currently approved NORVIR oral solution. The trial results indicated that the two formulations have comparable bioavailability. Additional studies evaluating vehicle effects, palatability, and human factors were also conducted to support approval.

While the two formulations have comparable bioavailability, the human factor study results showed multiple failures across critical tasks and across two user groups (caregivers and healthcare professionals) that could result in medication errors. These results and associated root cause analyses indicate that the user interface does not support safe and effective preparation of the proposed product for doses (b) (4)

Recommendation

The Office of Clinical Pharmacology has reviewed the information submitted in NDA 205912 and agrees that the powder formulation at doses (b) (4) 100 mg should be approved. (b) (4)

Summary of Clinical Pharmacology Studies

The following two clinical studies were submitted and reviewed to support the approval of NORVIR powder. An exploratory relative bioavailability study was also conducted (study 11-472) but will not be discussed in this review.

Study: 11-475: A Food Effect Assessment and Bioavailability Comparison of a Single-Dose of Ritonavir Oral Powder Relative to the Marketed Ritonavir Oral Solution in Healthy Adult Subjects)

Study Design: This was a single dose, open-label, randomized, cross-over study to compare the pharmacokinetics of ritonavir from 100 mg NORVIR powder (test) and oral solution (reference) under moderate-fat conditions in healthy volunteers (n=48). In addition, the effects of food (fasting or high fat breakfast) and vehicles (chocolate milk or pudding) on the pharmacokinetics of ritonavir were also determined following the administration of a 100 mg single dose NORVIR powder.

Results

- The test (NORVIR powder) to reference (NORVIR oral solution) ratios of geometric means with corresponding 90% CI for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were within the range of 80-125%.
- The bioavailability of NORVIR powder is decreased under fed conditions as compared to fasted conditions.
- The administration of the ritonavir oral powder in chocolate milk or in pudding did not have significant effects on the pharmacokinetics of ritonavir compared to administration in water under fed conditions.

Study: 12-279: A Comparison of the Single-Dose Bioavailability of Ritonavir Granules in Three Different Vehicles Relative to the Marketed Ritonavir Oral Solution in Healthy Adult Subjects

Study Design:

This was an open-label, randomized, cross-over study to compare the pharmacokinetics of 100 mg NORVIR powder in different vehicles (water, infant formula, or apple sauce) and oral solution under moderate-fat fed conditions in healthy volunteers (n=24).

Results: The administration of the ritonavir oral powder in water, infant formula, or apple sauce did not have significant effects on the pharmacokinetics of ritonavir compared to NORVIR oral solution.

Labeling Recommendations

Labeling negotiations have not been initiated at the time of this review.

Individual Study Review

Title: A Food Effect Assessment and Bioavailability Comparison of a Single-Dose of Ritonavir Oral Powder Relative to the Marketed Ritonavir Oral Solution in Healthy Adult Subjects (11-475)

Clinical Site: PPD Phase I Clinic, Austin TX

First Subject First Visit: 21 February 2013

Last Subject Last Visit: 21 April 2013

Objectives: To assess the bioequivalence of a ritonavir oral powder formulation to the reference marketed ritonavir oral solution under fed conditions. The study also assessed the effect of food and different vehicles on the bioavailability of the ritonavir oral powder formulation. The safety, tolerability, and palatability of ritonavir oral powder were also assessed.

Study Design

This was a Phase 1, single-dose, open-label, randomized study conducted according to a 6-regimen, 4-period, crossover design. Subjects were randomly assigned in equal numbers to receive 1 of 8 sequences of regimens. Doses in the 4 periods were separated by at least 5 days. Serial blood samples were collected for 36 hours after dosing in each period. Safety and tolerability were assessed throughout the study.

Regimen A: Single 100 mg dose of marketed ritonavir (Norvir®) oral solution administered under moderate-fat conditions (n=48)

Regimen B = Single 100 mg dose of ritonavir oral powder in water under moderate-fat conditions (n=48)

Regimen C = Single 100 mg dose of ritonavir oral powder in water under high-fat conditions (n=24)

Regimen D = Single 100 mg dose of ritonavir oral powder in water under fasting conditions (n=24)

Regimen E = Single 100 mg dose of ritonavir oral powder in chocolate milk under moderate-fat conditions (n=24)

Regimen F = Single 100 mg dose of ritonavir oral powder in vanilla-flavored pudding under moderate-fat conditions (n=24)

A moderate fat breakfast consisted of approximately 600 Kcal with approximately 30% from fat. A high fat breakfast content consisted of approximately 800 to 1000 Kcal, with approximately 60% from fat. In addition to the respective vehicle, each subject consumed approximately 240 mL of water.

Table 1. Study sequence and regimens

Sequence Group	Number of Subjects	Regimen ^a			
		Period 1	Period 2	Period 3	Period 4
I	6	A	B	C	D
II	6	B	A	C	D
III	6	A	B	D	C
IV	6	B	A	D	C
V	6	A	B	E	F
VI	6	B	A	E	F
VII	6	A	B	F	E
VIII	6	B	A	F	E

Key Inclusion/Exclusion Criteria

Adult healthy male and female subjects 18- 55 years of age (inclusive) with a body mass index (BMI) 19.0 – 29.0 kg/m² (inclusive) were eligible to enter the study. Subjects with history or presence of any illness or conditions that might confound the results of the study or poses an additional risk to the subject were excluded. The use of any medications (with the exception of oral/parenteral/transdermal hormonal contraceptives or hormonal replacement therapies for females) was not allowed within the 2-week period before study drug administration. Subjects were excluded if they had used CYP3A inducers or inhibitors within 1 month before study drug administration.

Identity of Investigational Products

Table 2. Identity of investigational products

	Ritonavir Regimens	
	A (Reference Formulation)	B, C, D, E, F (Test Formulation)
Dosage form	Oral solution	Oral powder for suspension (stickpacks)
Formulation	Marketed Norvir (US sourced)	Oral powder
Ritonavir content	80 mg/mL	15% (w/w)
Manufacturer	AbbVie	AbbVie
Manufacturing site	(b) (4)	
Bulk product lot number	13-000824/25073AF	13-000335
Finishing lot number	13-000906	13-000920
Expiration/Retest date	(b) (4)	
(b) (4)		

Pharmacokinetic Assessments

Blood samples for ritonavir assay were collected before dosing (0 hour) and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, and 36 hours after dosing in each study period. Values for the pharmacokinetic parameters of ritonavir were estimated using noncompartmental methods. C_{max} and T_{max} were determined directly from the plasma concentration-time data. The value of the apparent terminal phase elimination rate constant was obtained from the slope of the least squares linear regression of the logarithms of the plasma concentration versus time data from the terminal log-linear phase of the profile. The apparent oral clearance value (CL/F) was calculated by dividing the administered dose by the AUC_{inf}.

Bioanalysis

Plasma concentrations of ritonavir were determined using high-performance liquid chromatography method with tandem mass spectrometric detection (LC-MS/MS) by Abbvie. Samples quantified below the lowest standard were reported as zero.

Table 3. Summary of validated methods and bioanalytical QC results

Analyte	ritonavir
Internal standard	D ₅ -ritonavir
Matrix	Human Plasma
Extraction method	Liquid-liquid extraction
Calibration range	9.49 ng/mL – 1500 ng/mL
QC concentration	19.6, 139, 360, 781 and 1380 ng/mL
Inter-day precision (P) and accuracy (A)	P: 5.8% to 13.4% A: -2.8% to 2.2%
Storage stability	285 days at – 20 °C (maximum sample storage period: 75 days at – 20 °C)
Incurred Sample Reanalysis	95% (364/383) of the repeats met the acceptance criteria (b) (4)

Reviewer comments

It was noted that observed QC concentrations in certain runs were consistently lower than the nominal concentrations (3rd QC batch in Runs # 10, 11, 13, and 14, run dates from 17-Apr-2013 to 18-Apr-2013) by ~ 50%, suggesting potential errors during sample preparation or analysis, such as incorrect dilution of samples or internal standards. Upon information request, the Applicant responded that it was found that the internal standard was added twice to the second plate first column for some wells in those runs due to a programming error. Twelve study samples were also impacted by the programming error. Excluding these samples from the pharmacokinetic analysis did not change the overall conclusion of the study.

Results**Subject Disposition and Demographics**

For the 48 subjects who were enrolled, the mean age was 31.6 years (ranging from 20 to 53 years), the mean weight was 75.4 kg (ranging from 53.2 to 115.1 kg), and the mean height was 169.8 cm (ranging from 152.3 to 199.5 cm). There were 30 males (62.5%) and 18 females (37.5%) enrolled in the study. Thirty subjects were White (62.5%) and thirteen subjects were Black or African-American (27.1%). All 48 subjects completed study drug administration for all 4 study periods. Three subjects were on concomitant medications (ciprofloxacin, Mirena® IUD, or Depo-Provera®). These concomitant medications are not expected to alter the pharmacokinetics of ritonavir.

Pharmacokinetic Results**1. Summary of Ritonavir Pharmacokinetics**

The mean pharmacokinetic parameters of ritonavir in each Period are summarized in Table 4.

Table 4. Pharmacokinetic parameters of ritonavir

Regimen	A. Oral solution. Moderate fat	B. Powder in water. Moderate fat	C. Powder in water. High fat	D. Powder in water. Fasting	E. Powder in Chocolate Milk. Moderate fat	F. Powder in Pudding. Moderate fat
N	48	48	24	24	24	24
T _{max} (hr)	5 (2-10)	5 (3-10)	10 (5-18)	3 (2-5)	5 (2-10)	5 (3-12)
C _{max} (µg/mL)	0.43 (0.21)	0.44 (0.19)	0.40 (0.19)	0.80 (0.38)	0.36 (0.16)	0.44 (0.27)
AUC _t (µg·h/mL)	4.43 (1.87)	4.60 (1.98)	4.40 (1.76)	6.82 (2.90)	4.00 (1.79)	4.67 (2.56)
AUC _{inf} (µg·h/mL)	4.60 (1.94)	4.90 (2.03)	4.64 (1.90)	6.96 (2.95)	4.18 (1.87)	4.85(2.62)
Half life (hr)	5.79 (1.07)	6.17 (1.14)	5.95 (1.28)	5.32 (1.07)	6.29 (1.24)	5.76 (1.77)
CL/F (L/h)	26.41 (13.02)	25.44 (11.98)	24.73 (9.20)	17.12 (7.54)	29.32 (13.95)	26.80 (13.45)

Data are expressed as arithmetic mean (standard deviation) except Tmax [median (range)]

2. Statistical Analysis for Relative Bioavailability

The statistical analysis of relative bioavailability for ritonavir is summarized in Table 5.

1. Relative bioavailability of ritonavir powder compared to ritonavir oral solution.

The two formulations are bioequivalent under fed conditions. The test to reference ratios of geometric means with corresponding 90% CI for C_{max}, AUC_{0-t} and AUC_{0-∞} were within the range of 80-125%.

2. Food effects

The bioavailability of NORVIR powder is decreased under fed conditions as compared to fasted conditions. Relative to fasting, administration of NORVIR powder with a moderate fat meal decreased ritonavir C_{max} and AUC_{inf} values by 39% and 23%, respectively. Relative to moderate fat meal, administration of NORVIR powder with a high fat meal further decreased ritonavir C_{max} and AUC_{inf} values by 12% and 17%, respectively.

Reviewer comments: This is qualitatively consistent with other formulations of NORVIR (tablet and oral solution). Despite the decrease in the exposures of ritonavir under fed conditions, all NORVIR formulations are to be administered under fed conditions to manage gastrointestinal adverse events.

3. Vehicle effects

Under moderate-fat conditions, administration of the ritonavir oral powder in chocolate milk or in pudding did not have significant effects on the pharmacokinetics of ritonavir compared to administration in water. Ritonavir powder may be mixed with chocolate milk or pudding for administration.

Table 5. Relative bioavailability and 90% confidence intervals of ritonavir pharmacokinetic parameters across dosing regimens

Dosing Regimen	Pharmacokinetic Parameter	Central Value ^a		Relative Bioavailability	
		Test	Reference	Point Estimate ^b	90% Confidence Interval
Bioequivalence Assessment					
A vs. B (Powder vs. Oral Solution)	C _{max}	393.31	386.68	1.017	0.947–1.092
	AUC _t	4150.49	4022.20	1.032	0.982–1.084
	AUC _∞	4356.22	4194.49	1.039	0.992–1.087
Food Effect Assessment					
C vs. D (High Fat vs. Fasting)	C _{max}	361.88	715.60	0.506	0.440–0.581
	AUC _t	4107.41	6245.61	0.658	0.608–0.711
	AUC _∞	4322.62	6386.59	0.677	0.629–0.728
C vs. B (High Fat vs. Moderate Fat)	C _{max}	361.88	433.68	0.834	0.729–0.955
	AUC _t	4107.41	4683.88	0.877	0.798–0.963
	AUC _∞	4322.62	4896.35	0.883	0.807–0.966
B vs. D (Moderate Fat vs. Fasting)	C _{max}	433.68	715.60	0.606	0.535–0.686
	AUC _t	4683.88	6245.61	0.750	0.692–0.812
	AUC _∞	4896.35	6386.59	0.767	0.709–0.829
Vehicle Effect Assessment					
E vs. A (Powder in Chocolate Milk vs. Oral Solution)	C _{max}	319.93	328.85	0.973	0.871–1.086
	AUC _t	3615.19	3446.24	1.049	0.960–1.147
	AUC _∞	3783.13	3613.64	1.047	0.961–1.141
F vs. A (Powder in Pudding vs. Oral Solution)	C _{max}	379.46	328.85	1.154	1.033–1.288
	AUC _t	4067.21	3446.24	1.180	1.080–1.290
	AUC _∞	4238.06	3613.64	1.173	1.077–1.278
E vs. B (Powder in Chocolate Milk vs. Powder in Water)	C _{max}	319.93	356.70	0.897	0.803–1.001
	AUC _t	3615.19	3677.84	0.983	0.899–1.074
	AUC _∞	3783.13	3875.68	0.976	0.896–1.063

Conclusion

- NORVIR powder (test) and oral solution (reference) are bioequivalent under fed conditions.
- The bioavailability of NORVIR powder is decreased under fed conditions as compared to fasted conditions.
- The administration of the ritonavir oral powder in chocolate milk or in pudding did not have significant effects on the pharmacokinetics of ritonavir compared to administration in water under moderate fat conditions.

Study Title: A Comparison of the Single-Dose Bioavailability of Ritonavir Granules (powder) in Three Different Vehicles Relative to the Marketed Ritonavir Oral Solution in Healthy Adult Subjects (12-293)

First Subject First Visit: 23 January 2012

Last Subject Last Visit: 11 March 2012

Study Site: (b) (4)

Objective

The objective of this study was to compare the bioavailability of a single (100 mg) dose of a ritonavir powder test formulation in 3 different vehicles, (water, infant formula and apple sauce) with that of the reference marketed ritonavir oral solution (100 mg dose) under fed conditions. The safety, tolerability and palatability of the ritonavir powder in the 3 vehicles were also assessed.

Study Design

This Phase 1, single-dose, non-fasting, open-label, randomized, study was conducted according to a 4-period, crossover design in 24 healthy volunteers. Each dose of study drug (a single dose of 100 mg ritonavir) was taken orally approximately 30 minutes after starting a moderate-fat breakfast (approximately 30% of the calories from fat). In addition to the respective vehicle, each subject consumed approximately 240 mL of water. A washout period between the treatments was at least 5 days.

Regimen A: 100 mg ritonavir powder mixed in water

Regimen B: 100 mg ritonavir powder mixed in infant formula

Regimen C: 100 mg ritonavir powder mixed in applesauce

Regimen D: 100 mg single dose of marketed ritonavir (Norvir®) oral solution

Identity of Investigational Products

Table 1. Identity of investigational products

	Ritonavir Regimens	
	A, B, C (Test)	D (Reference)
Dosage Form	Granules	Oral solution
Formulation	Uncoated Granules	Norvir®
Strength	15% ^a	80 mg/mL
Bulk Product Lot Number	11-005386	12-000140
Finishing lot	12-000132	12-000134
Mode of Administration	Oral	Oral
Potency (% of Label Claim)	(b) (4)	(b) (4)
Expiration/Retest Date	(b) (4)	(b) (4)
Batch Size	(b) (4)	(b) (4)
Excipients	(b) (4)	(b) (4)

a. Ritonavir content, w/w.

Key Inclusion/Exclusion Criteria

Adult healthy male and female subjects 18- 55 years of age (inclusive), with a body mass index (BMI) $18 < 30 \text{ kg/m}^2$ were eligible to enter the study. Subjects with history or presence of any illness or conditions that might confound the results of the study or poses an additional risk to the subject were excluded. The use of any medications was not allowed within the 2-week period before study drug administration. Subjects were excluded if they had used CYP3A inducers or inhibitors within 1 month before study drug administration.

Pharmacokinetic Assessments

Blood samples for ritonavir assay were collected before dosing (0 hour) and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, and 36 hours after dosing in each study period. Values for the pharmacokinetic parameters of ritonavir were estimated using noncompartmental methods. C_{max} and T_{max} were determined directly from the plasma concentration-time data. The value of the apparent terminal phase elimination rate constant was obtained from the slope of the least squares linear regression of the logarithms of the plasma concentration versus time data from the terminal log-linear phase of the profile. The apparent oral clearance value (CL/F) was calculated by dividing the administered dose by the AUC_{inf} .

Bioanalysis

Plasma concentrations of ritonavir were determined using a high-performance liquid chromatography method with tandem mass spectrometric detection (LC-MS/MS) by Abbvie. Samples quantified below the lowest standard were reported as zero. Overall, the method was adequately validated. The standard curve and QC data indicated that assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

Table 2. Summary of bioanalytical method and QC results

Analyte	ritonavir
Internal standard	D ₅ -ritonavir
Matrix	Human Plasma
Extraction method	Liquid-liquid extraction
Calibration range	9.81 – 8180 ng/mL
QC concentration	21.1, 527, 6580 ng/mL
Inter-day precision (P) and accuracy (A)	P: 4.4% to 5.7% A: -1.4% to 3.1%
Storage stability	285 days at – 20 °C (maximum sample storage period: 171 days at – 20 °C)
Incurred Sample Reanalysis [#]	98% (182/186) of the repeats met the acceptance criteria (b) (4)

[#]ISR was repeated using a narrow quantitation range (9.49 ng/mL – 1500 ng/mL) after a leak error. Repeated ISR showed that 177/186 of the repeats met the acceptance criteria (b) (4)

Results

Disposition of Subjects and Demographics

Twenty four subjects were enrolled in the study and 23 subjects (14 males and 9 females) completed all four periods of the study. Subject 106 received Regimen B (ritonavir powder in infant formula) in Period 1 but was discontinued from the study prior to dosing in Period 2 due to a positive cotinine test. All available data from all 24 subjects were included in the statistical analyses of the pharmacokinetic parameters

Table 3. Demographic summary for all randomized subjects

	Mean \pm SD (N = 24)	Min - Max
Age (years)	37.3 \pm 10.91	19 - 55
Weight (kg)	72.2 \pm 11.98	55 - 99
Height (cm)	169.7 \pm 9.95	153 - 197
Sex	15 Males (62.5%), 9 Females (37.5%)	
Race	19 White (79.2%), 5 Black (20.8%)	

SD = Standard deviation.

Pharmacokinetic Results and Conclusion

Ritonavir plasma concentration-time profiles, the summary of pharmacokinetics of ritonavir in each period, and statistical analysis are presented below. The test Regimens A, B and C (ritonavir powder in water, infant formula and applesauce, respectively) showed comparable relative bioavailability to the reference Regimen D (ritonavir oral solution). Ritonavir powder can be reconstituted in water, infant formula or apple sauce.

Fig 1. Mean \pm SD ritonavir plasma concentration-time profiles

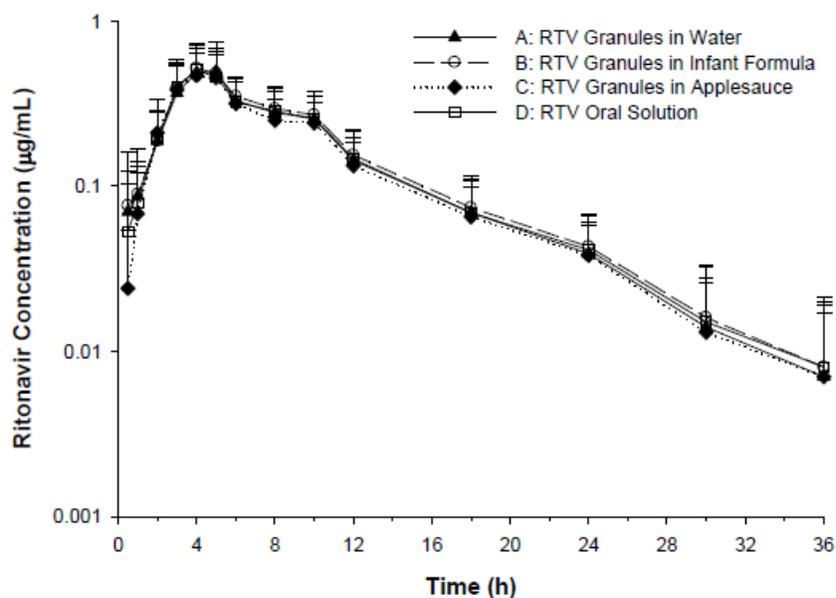


Table 4. Summary of pharmacokinetic parameters of ritonavir

Pharmacokinetic Parameters (Units)		Regimens ^a			
		A: Test RTV Granules in Water (N = 23)	B: Test RTV Granules in Infant Formula (N = 24)	C: Test RTV Granules in Applesauce (N = 23)	D: Reference RTV Oral Solution (N = 23)
T _{max} ^b	(h)	5 (3 – 10)	4 (3 – 10)	4 (3 – 5)	4 (3 – 8)
C _{max}	(µg/mL)	0.54 ± 0.25	0.55 ± 0.19	0.50 ± 0.18	0.53 ± 0.024
AUC _t	(µg•h/mL)	4.49 ± 1.64	4.75 ± 1.53	4.24 ± 1.40	4.53 ± 1.85
AUC _∞	(µg•h/mL)	4.64 ± 1.66	4.91 ± 1.55	4.41 ± 1.42	4.71 ± 1.86
t _{1/2} ^c	(h)	5.52 ± 1.19 ^d	5.61 ± 1.16	5.70 ± 1.19	5.95 ± 1.10
CL/F ^e	(L/h)	24.9 ± 10.5	22.8 ± 8.58	25.4 ± 9.44	25.1 ± 11.1

- All four regimens were administered as a 100 mg dose.
- T_{max} is presented as median (min – max). Statistics for were performed on mean T_{max}.
- Harmonic mean ± pseudo-standard deviation; evaluations of t_{1/2} were based on statistical tests for β.
- β was statistically significantly different from reference regimen (Regimen D, mixed effects analysis, p < 0.05).
- Parameter was not tested statistically.

Table 5. Relative bioavailability and 90% confidence intervals (A: NORVIR powder in water, B: NORVIR powder in infant formula, C: NORVIR powder in apple sauce, D: NORVIR oral solution)

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value ^a		Relative Bioavailability	
		Test	Reference	Point Estimate ^b	90% Confidence Interval
A vs. D	C _{max}	0.49	0.49	1.001	0.901 – 1.112
	AUC _t	4.26	4.24	1.005	0.938 – 1.077
	AUC _∞	4.42	4.43	0.998	0.934 – 1.066
B vs. D	C _{max}	0.51	0.49	1.054	0.961 – 1.156
	AUC _t	4.48	4.24	1.059	0.989 – 1.133
	AUC _∞	4.66	4.43	1.051	0.985 – 1.122
C vs. D	C _{max}	0.47	0.49	0.965	0.880 – 1.059
	AUC _t	4.08	4.24	0.964	0.901 – 1.031
	AUC _∞	4.25	4.43	0.960	0.900 – 1.023

- Antilogarithm of the least squares means for logarithms.
- Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SU-YOUNG CHOI
05/09/2017

SHIRLEY K SEO
05/09/2017