

ARK™ Voriconazole II Assay

This ARK Diagnostics, Inc. package insert for the ARK Voriconazole II Assay must be read carefully prior to use. Package insert instructions must be followed accordingly. Reliability of the assay results cannot be guaranteed if there are any deviations from the instructions in this package insert. The ARK Voriconazole II Assay test system includes separately provided test kits for the ARK Voriconazole II Assay, ARK Voriconazole II Calibrator and ARK Voriconazole II Control.

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





Emergo Europe

Westervoortsedijk 60

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KEY TO SYMBOLS USED

| | | | |
|------------------------------------------------------------------------------------|------------------------------------|---------------------------------------------------------------------------------------------------|------------------------|
|  | Batch code |  YYYY-MM-DD | Use by/Expiration date |
|  | Catalog Number |  | Manufacturer |
|  | Authorized Representative |  | CE Mark |
|  | In Vitro Diagnostic Medical Device |  | Temperature limitation |
|  | Consult Instructions for Use |  | Reagent 1/ Reagent 2 |
| Rx Only | For Prescription Use Only | | |

1 NAME

ARK™ Voriconazole II Assay

2 INTENDED USE

The ARK Voriconazole II Assay is a homogeneous enzyme immunoassay intended for the quantitative determination of voriconazole in human serum on automated clinical chemistry analyzers. The measurements obtained are used in monitoring levels of voriconazole to ensure appropriate therapy. The assay should only be used in conjunction with information available from clinical evaluations and other diagnostic procedures.

Caution: Federal Law restricts this device to sale by or on the order of a licensed practitioner.

3 SUMMARY AND EXPLANATION OF THE TEST

Voriconazole (VFEND®, Pfizer) is a triazole antifungal agent and is designated chemically as (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H-1,2,4-triazol-1-yl)-2-butanol.¹ VFEND is a triazole antifungal drug indicated for use in the treatment of:

- Invasive aspergillosis
- Candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds
- Esophageal candidiasis
- Serious infections caused by *Scedosporium apiospermum* and *Fusarium* spp. including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy

4 PRINCIPLES OF THE PROCEDURE

ARK Voriconazole II Assay is a homogeneous immunoassay based on competition between drug in the specimen and voriconazole labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for binding to the antibody reagent. As the latter binds antibody, enzyme activity decreases. In the presence of drug from the specimen, enzyme activity increases and is directly proportional to the drug concentration. Active enzyme converts the coenzyme nicotinamide adenine dinucleotide (NAD) to NADH that is measured spectrophotometrically as a rate of change in absorbance. Endogenous serum G6PDH does not interfere with the results because the coenzyme NAD functions only with the bacterial enzyme used in the assay.

5 REAGENTS

| REF | Product Description | Quantity/Volume |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| 5030-0001-01 | ARK Voriconazole II Assay Reagent [R1] – Antibody/Substrate rabbit polyclonal antibodies to voriconazole, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers | 1 X 28 mL |
| | Reagent [R2] – Enzyme Voriconazole labeled with bacterial G6PDH, buffer, bovine serum albumin, sodium azide, and stabilizers | 1 X 14 mL |

Reagent Handling and Storage

ARK Voriconazole II Assay reagents are provided liquid, ready to use and may be used directly from the refrigerator. When not in use, reagents must be stored at 2–8°C (36–46°F), upright and with screw caps tightly closed. If stored as directed, reagents are stable until the expiration date printed on the label. Do not freeze reagents. Avoid prolonged exposure to temperatures above 32°C (90°F). **Improper storage of reagents can affect assay performance.** Reagents were stable up to 60 days when stored on-board the instrument based on supporting data.

ARK Voriconazole products contain ≤0.09% sodium azide. As a precaution, affected plumbing including instrumentation should be flushed adequately with water to mitigate the potential accumulation of explosive metal azides. No special handling is required regarding other assay components.

6 WARNINGS AND PRECAUTIONS

- For In Vitro Diagnostic Use. For prescription use only.
- Reagents [R1] and [R2] are provided as a matched set and should not be interchanged with reagents from different lot numbers.
- Reagents contain ≤0.09% sodium azide.
- The assay should only be used in conjunction with information available from clinical evaluations and other diagnostic procedures.

7 SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

- Serum is required. A steady state, trough (pre-dose) sample is generally accepted as most consistent for therapeutic drug monitoring of voriconazole. Time of blood draw since last dose should be noted.

- Blood collection must be performed with collection tubes compatible for use with therapeutic drug monitoring (TDM).
- Do not induce foaming and avoid repeated freezing and thawing to preserve the integrity of the specimen from the time it is collected until the time it is assayed.
- Fibrin, red blood cells, and other particulate matter may cause an erroneous result. Ensure adequate centrifugation.
- Clarified specimens may be stored up to one week at 2 to 8°C. If testing will be delayed more than one week, specimens should be stored frozen ($\leq -20^{\circ}\text{C}$) up to four weeks prior to being tested. Care should be taken to limit the number of freeze-thaw cycles.
- **Handle all patient specimens as if they were potentially infectious.**

8 PROCEDURE

Materials Provided

ARK Voriconazole II Assay – [REF] 5030-0001-01

Materials Required – Provided Separately

ARK Voriconazole II Calibrator – [REF] 5030-0002-01

Quality Controls – ARK Voriconazole II Control – [REF] 5030-0003-01

Instruments

Reagents [R1] and [R2] may need to be transferred to analyzer-specific reagent containers prior to use. Avoid cross-contamination of [R1] and [R2].

Assay Sequence

To run or calibrate the assay, see the instrument-specific operator's manual and instrument-specific application sheet.

Calibration

Perform a full calibration (6-point) procedure using the ARK Voriconazole II Calibrators A, B, C, D, E, and F; test calibrators in duplicate. Verify the calibration curve with at least two levels of quality controls according to the established laboratory quality assurance plan. CAL A is the calibration blank.

Recalibrate whenever a new lot of reagents is used or as indicated by quality control results (See Quality Control below). Acceptable quality control results are needed to validate a new calibration curve. If a new set of reagents with the same lot number is used, validate the system by assaying controls.

A stored calibration curve was effective up to at least 30 days based on supporting data.

Quality Control (QC)

Laboratories should establish QC procedures for the ARK Voriconazole II Assay. All quality control requirements and testing should be performed in conformance with local, state and/or federal regulations or accreditation requirements. Ensure that the quality control results meet the acceptance criteria before reporting patient results.

Good laboratory practice suggests that at least two levels (low and high medical decision points) of quality control be tested each day patient samples are assayed and each time a calibration is performed. Monitor the control values for any trends or shifts. If any trends or shifts are detected, or if the control does not recover within the specified range, review all operating parameters according to your clinical laboratory quality procedures. Contact Customer Service for further assistance.

Manual Dilution Protocol

The measurement range of the ARK Voriconazole II Assay is 0.5 – 14.0 $\mu\text{g/mL}$. Specimens containing voriconazole in higher concentrations ($>14.0 \mu\text{g/mL}$) are assayed by dilution of the specimen into the measurement range. Dilute the specimen with zero calibrator (CAL A). A four-fold dilution factor is suggested. Multiply the assayed result by the dilution factor.

$$\text{Manual Dilution Factor} = \frac{\text{Volume of Specimen} + \text{Volume of CAL A}}{\text{Volume of Specimen}}$$

9 RESULTS

Report result units as $\mu\text{g/mL}$ or $\mu\text{mol/L}$. To convert results from $\mu\text{g/mL}$ voriconazole to $\mu\text{mol/L}$ voriconazole, multiply $\mu\text{g/mL}$ by 2.863. The voriconazole value from this assay should be used in conjunction with other clinical information. Refer to the instrument specific operator's manual for any result error codes.

A therapeutic range for voriconazole has not been well established. The reference range of 1.0 $\mu\text{g/mL}$ to 5.5 $\mu\text{g/mL}$ has been proposed.² The assay should only be used in conjunction with information available from clinical evaluations and other diagnostic procedures. **Refer to Expected Values.**

10 LIMITATIONS OF PROCEDURE

This assay is designed for use with serum; refer to the sections **Specimen Collection and Preparation for Analysis**. It is generally good practice to use the same method (as well as matrix) consistently for individual patient care due to the potential for method-to-method variabilities. See the section **Expected Values** below.

11 EXPECTED VALUES

A therapeutic range for voriconazole has not been well established. The reference range of 1.0 $\mu\text{g/mL}$ to 5.5 $\mu\text{g/mL}$ has been proposed.² Steady state concentrations may be achieved after 5 to 7 days of treatment. Practice guidelines³⁻⁵ support TDM and clinical application of TDM has been recommended⁶⁻⁸ due to the high inter-individual and intra-individual variation in the metabolism⁹⁻¹⁰ of voriconazole, non-linear pharmacokinetics and CYP2C19 polymorphisms.¹¹⁻¹² Voriconazole treatment has been used for invasive fungal infection and prophylactically in transplant patients.¹³⁻¹⁵ Consideration should be given to the requirements for pediatric use, since metabolism in children may be different than for adults.¹⁶⁻¹⁸

Voriconazole drug concentrations should not be the only means of therapeutic drug management. The assay should be used in conjunction with information available from clinical evaluations and other diagnostic procedures. Clinicians should carefully monitor patients during therapy and dosage adjustments.

12 SPECIFIC PERFORMANCE CHARACTERISTICS

Each laboratory is responsible for verification of performance using instrument parameters established for their analyzer. The following performance characteristics were obtained on the Roche cobas® c 501 System.

Sensitivity

Limit of Quantitation (LOQ)

The following characteristics were determined according to CLSI EP17-A2 for the ARK Voriconazole II Assay. Analyzer-specific performance may vary.

| Criterion | Voriconazole Concentration ($\mu\text{g/mL}$) |
|---------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| Limit of Blank (LoB); N = 60 $\mu\text{B} + 1.645 \text{ SD}$, where $\text{SD} = 0.002$ | 0.003 |
| Limit of Detection (LoD); N = 60 $\text{LoB} + 1.652 \text{ SD}$, where $\text{SD} = 0.023$ | 0.04 |
| Limit of Quantitation (LoQ); N = 40 $\text{LoQ} - 2 \text{ SD} > \text{LoD}$ With acceptable recovery and linearity | 0.50 |

Each laboratory is responsible for determining reporting criteria for voriconazole concentrations. The following suggestion from CLSI EP17-A2 may be appropriate:

Result \leq LoB report "not detected; concentration $<$ LoD"

LoB $<$ Result $<$ LoQ report "analyte detected; concentration $<$ LoQ"

Result \geq LoQ report the result as measured

Summary of Mean Voriconazole and Precision for LoB/LoD/LoQ Samples: Human serum from 20 individuals (patients not treated with voriconazole) were tested once per day for 3 days (N=60) for determination of reproducibility of the Blank. Human serum from patients treated with voriconazole was pooled to obtain voriconazole levels 0.20, 0.30, 0.40, 0.50 and 0.70 $\mu\text{g/mL}$ as determined by LC-MS/MS. Twenty replicates of 0.20 $\mu\text{g/mL}$ were tested per day for 3 days (N=60). Eight replicates were tested once per day for 5 days (N=40) for the remaining voriconazole-positive levels. All samples were tested with 3 different lots of the ARK Voriconazole II Assay. The LoQ (0.5 $\mu\text{g/mL}$) was assured for each lot.

| | Level ($\mu\text{g/mL}$) | 0.00 | 0.20 | 0.30 | 0.40 | 0.50 | 0.70 |
|-------------|----------------------------|-------|-------|-------|-------|-------|-------|
| | N | 60 | 60 | 40 | 40 | 40 | 40 |
| Lot 1 | Mean | 0.00 | 0.20 | 0.29 | 0.39 | 0.47 | 0.69 |
| | RMSSD | 0.001 | 0.023 | 0.027 | 0.022 | 0.027 | 0.034 |
| | %CV | NA | 11.4 | 9.6 | 5.6 | 5.8 | 4.9 |
| Lot 2 | Mean | 0.00 | 0.19 | 0.29 | 0.40 | 0.47 | 0.67 |
| | RMSSD | 0.000 | 0.020 | 0.020 | 0.031 | 0.021 | 0.039 |
| | %CV | NA | 10.4 | 7.0 | 7.8 | 4.5 | 5.8 |
| Lot 3 | Mean | 0.00 | 0.22 | 0.33 | 0.43 | 0.52 | 0.73 |
| | RMSSD | 0.002 | 0.014 | 0.013 | 0.018 | 0.017 | 0.024 |
| | %CV | NA | 6.3 | 4.0 | 4.1 | 3.2 | 3.3 |
| Lot Average | | 0.00 | 0.20 | 0.30 | 0.41 | 0.49 | 0.70 |

Measurement Range

The measurement range of the ARK Voriconazole II Assay is 0.5 – 14.0 $\mu\text{g/mL}$. Specimens containing voriconazole in higher concentrations ($>14.0 \mu\text{g/mL}$) may be assayed by dilution of the specimen into the measurement range for a quantitative result or otherwise reported as detected above the measurement range. Refer to **Section 8 Procedure - Manual Dilution Protocol**.

Recovery

Analytical recovery was assessed by adding concentrated voriconazole drug into human serum negative for voriconazole. A stock concentrate of voriconazole in methanol was added volumetrically to human serum negative for voriconazole, representing drug concentrations across the assay range. Six replicates of each sample were assayed. The results were averaged and compared to the target concentration and percent recovery calculated.

$$\% \text{ Recovery} = \frac{100 \times \text{Mean recovered concentration}}{\text{Theoretical concentration}}$$

| Theoretical Concentration (µg/mL) | Mean Recovered Concentration (µg/mL) | Percent Recovery |
|-----------------------------------|--------------------------------------|------------------|
| 0.5 | 0.45 | 90.0 |
| 1.2 | 1.19 | 99.2 |
| 3.0 | 3.05 | 101.7 |
| 6.0 | 5.86 | 97.7 |
| 9.0 | 8.74 | 97.1 |
| 12.0 | 11.44 | 95.3 |
| 15.0 | 15.75 | 105.0 |

Mean percent recovery: 98.0

Linearity

Linearity studies were performed as suggested in CLSI/NCCLS Protocol EP6-A. A 20.0 µg/mL voriconazole serum sample was prepared and dilutions were made proportionally with human serum negative for voriconazole. Linearity at specific dilutions was considered acceptable if the percent difference was ±10% between the predicted 1st and 2nd order regressed values, or ≤ 0.2 µg/mL at concentrations ≤ 2.0 µg/mL. A linear relationship was demonstrated between 0.5 and 16.0 µg/mL ($y = 1.0209x - 0.0416$).

| Nominal (µg/mL) | Measured Results (µg/mL) | 1st Order Predicted Results | 2nd Order Predicted Results | Difference |
|-----------------|--------------------------|-----------------------------|-----------------------------|------------|
| 0.0 | 0.00 | -0.04 | 0.02 | NA |
| 0.5 | 0.43 | 0.47 | 0.51 | 0.04 µg/mL |
| 1.0 | 1.02 | 0.98 | 1.01 | 0.03 µg/mL |
| 2.0 | 2.05 | 2.00 | 2.00 | 0.00 µg/mL |
| 4.0 | 4.21 | 4.04 | 4.00 | -1.0% |
| 6.0 | 5.89 | 6.08 | 6.02 | -1.1% |
| 8.0 | 8.08 | 8.13 | 8.06 | -0.9% |
| 10.0 | 9.91 | 10.17 | 10.11 | -0.6% |
| 12.0 | 12.26 | 12.21 | 12.18 | -0.2% |
| 14.0 | 14.43 | 14.25 | 14.28 | 0.2% |
| 16.0 | 16.31 | 16.29 | 16.39 | 0.6% |
| 20.0* | 21.94 | NA | NA | NA |

*Above the measurement range

Precision

Precision was determined as described in CLSI Protocol EP5-A3. Tri-level controls and three samples of voriconazole in pooled human serum were used in the study. Each level was assayed in quadruplicate twice a day for 20 days. Each of the runs per day was separated by at least two hours. The within run, between day, total SD, and percent CVs were calculated. Results are shown below. Acceptance criteria: ≤10% total CV.

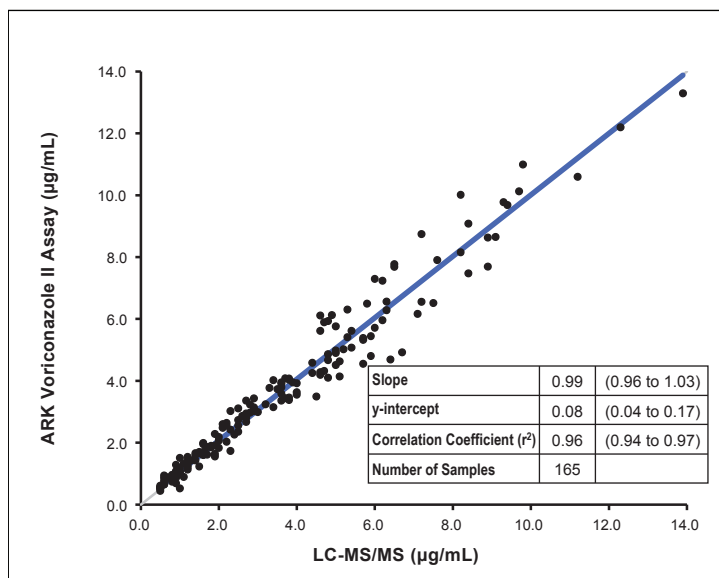
| Sample | N | Mean (µg/mL) | Repeatability Within Run | | Between Run | | Between Day | | Reproducibility Total | |
|-----------------------------|-----|--------------|--------------------------|--------|-------------|--------|-------------|--------|-----------------------|--------|
| | | | SD | CV (%) | SD | CV (%) | SD | CV (%) | SD | CV (%) |
| ARK Voriconazole II Control | | | | | | | | | | |
| LOW | 160 | 1.03 | 0.047 | 4.6 | 0.030 | 2.9 | 0.022 | 2.1 | 0.051 | 4.9 |
| MID | 160 | 4.91 | 0.194 | 3.9 | 0.124 | 2.5 | 0.101 | 2.1 | 0.209 | 4.3 |
| HIGH | 160 | 9.39 | 0.394 | 4.2 | 0.242 | 2.6 | 0.207 | 2.2 | 0.426 | 4.5 |
| Human Serum | | | | | | | | | | |
| LOW | 160 | 1.02 | 0.043 | 4.2 | 0.029 | 2.8 | 0.024 | 2.4 | 0.047 | 4.6 |
| MID | 160 | 5.03 | 0.182 | 3.6 | 0.149 | 3.0 | 0.111 | 2.2 | 0.217 | 4.3 |
| HIGH | 160 | 9.80 | 0.334 | 3.4 | 0.286 | 2.9 | 0.221 | 2.3 | 0.407 | 4.2 |

Serum was collected from voriconazole-treated patients and pooled to prepare three concentration levels. Each level was assayed in quadruplicate twice a day for 5 days. Each of the runs per day was separated by at least two hours. Testing was performed by three independent lots of the ARK Voriconazole II Assay. Total precision ranged from 3.3 to 6.9 %CV among all levels and lots tested.

| Sample | N | Mean (µg/mL) | Repeatability Within Run | | Between Run | | Between Day | | Reproducibility Total | |
|--------|----|--------------|--------------------------|--------|-------------|--------|-------------|--------|-----------------------|--------|
| | | | SD | CV (%) | SD | CV (%) | SD | CV (%) | SD | CV (%) |
| Lot 1 | | | | | | | | | | |
| LOW | 40 | 1.03 | 0.053 | 5.2 | 0.041 | 4.0 | 0.032 | 3.1 | 0.062 | 6.0 |
| MID | 40 | 4.95 | 0.237 | 4.8 | 0.095 | 1.9 | 0.077 | 1.6 | 0.243 | 4.9 |
| HIGH | 40 | 10.58 | 0.660 | 6.2 | 0.391 | 3.7 | 0.360 | 3.4 | 0.728 | 6.9 |
| Lot 2 | | | | | | | | | | |
| LOW | 40 | 0.96 | 0.040 | 4.2 | 0.045 | 4.7 | 0.038 | 3.9 | 0.058 | 6.0 |
| MID | 40 | 4.80 | 0.271 | 5.7 | 0.106 | 2.2 | 0.064 | 1.3 | 0.271 | 5.7 |
| HIGH | 40 | 10.69 | 0.574 | 5.4 | 0.296 | 2.8 | 0.252 | 2.4 | 0.604 | 5.7 |
| Lot 3 | | | | | | | | | | |
| LOW | 40 | 0.99 | 0.030 | 3.1 | 0.018 | 1.8 | 0.011 | 1.1 | 0.033 | 3.3 |
| MID | 40 | 4.76 | 0.186 | 3.9 | 0.085 | 1.8 | 0.060 | 1.3 | 0.186 | 3.9 |
| HIGH | 40 | 10.50 | 0.625 | 6.0 | 0.321 | 3.1 | 0.299 | 2.8 | 0.677 | 6.5 |

Method Comparison

Method comparison studies were performed using CLSI Protocol EP9-A3 as a guideline. Results from the ARK Voriconazole II Assay were compared with results from LC-MS/MS. Passing-Bablok regression analysis was performed for 165 serum specimens with voriconazole concentrations by LC-MS/MS that ranged 0.5 µg/mL to 13.9 µg/mL. Passing-Bablok¹⁹ regression statistics are shown below (with 95% confidence limits).



Interfering Substances

Interference studies were conducted using CLSI Protocol EP7-A2 as a guideline. Clinically high concentrations of the following potentially interfering substances in serum with known levels of voriconazole (1.0 and 5.0 µg/mL) were evaluated. Each sample was assayed using the ARK Voriconazole II Assay, along with a serum control of voriconazole. Measurement of voriconazole resulted in ≤10% error in the presence of interfering substances at the levels tested.

| Interfering Substance | Interferent Concentration | Percentage Recovery | |
|--------------------------|---------------------------|------------------------|------------------------|
| | | 1.0 µg/mL Voriconazole | 5.0 µg/mL Voriconazole |
| Albumin | 12 g/dL | 104.5 | 98.8 |
| Bilirubin - conjugated | 70 mg/dL | 99.4 | 99.7 |
| Bilirubin - unconjugated | 70 mg/dL | 103.4 | 95.9 |
| Cholesterol | 617 mg/dL | 95.8 | 98.3 |
| Gamma-Globulin | 12 g/dL | 106.3 | 97.9 |
| Hemoglobin | 1000 mg/dL | 103.0 | 93.5 |
| Rheumatoid Factor | 1000 IU/mL | 103.5 | 100.1 |
| Triglycerides | 1000 mg/dL | 107.2 | 99.2 |
| Uric Acid | 30 mg/dL | 105.5 | 96.2 |

Specificity

Metabolism

Voriconazole displays highly variable non-linear pharmacokinetics, which are primarily due to polymorphic CYP2C19 metabolism. After oral and intravenous administration voriconazole is extensively metabolized to inactive metabolites including *N*-oxide voriconazole, 4-hydroxy-voriconazole and di-hydroxy-voriconazole. Voriconazole and its major metabolite, *N*-oxide voriconazole, are present quantitatively in serum²⁰, while hydroxylated metabolites are easily excreted into urine. The concentration of *N*-oxide metabolite usually does not exceed concentration of the parent drug. Pharmacokinetics of voriconazole may be further influenced by other drug metabolizing enzymes and age-based differences in drug metabolism.

Metabolite

The crossreactivity of *N*-oxide voriconazole metabolite (5.0 µg/mL or 10.0 µg/mL) in the ARK Voriconazole II Assay was not clinically significant ($\leq 3.0\%$ crossreactivity) when tested in the absence (0.0 µg/mL) or presence of voriconazole (1.0 µg/mL or 5.0 µg/mL) in human serum.

| N-oxide-VRZ (µg/mL) | Measured Voriconazole in Absence/Presence of Metabolite (µg/mL) | | |
|---------------------|-----------------------------------------------------------------|----------------------------------|----------------------------------|
| | Voriconazole Absent (0.0 µg/mL) | Voriconazole Present (1.0 µg/mL) | Voriconazole Present (5.0 µg/mL) |
| 0.0 | 0.00 | 1.06 | 4.99 |
| 5.0 | 0.04 | 1.17 | 4.96 |
| 10.0 | 0.10 | 1.23 | 5.29 |

Crossreactivity

The compounds listed below did not interfere with the ARK Voriconazole II Assay when tested in the absence (0.0 µg/mL) or presence of voriconazole (1.0 µg/mL and 5.0 µg/mL). Levels tested were at or above maximum physiological or pharmacological concentrations. Voriconazole concentrations of samples containing interferent were compared to the voriconazole level in a normal serum control.

| Compound | Concentration (µg/mL) | Compound | Concentration (µg/mL) |
|-----------------------|-----------------------|-------------------|-----------------------|
| Abacavir | 30 | Lopinavir | 30 |
| Acetaminophen | 200 | Lorazepam | 10 |
| Alprazolam | 5 | Maraviroc | 10 |
| Amikacin | 100 | Meropenem | 500 |
| Amphotericin | 100 | Methotrexate | 100 |
| Amprenavir | 30 | Metronidazole | 200 |
| Atazanavir | 30 | Micafungin | 300 |
| Atovaquone | 100 | Morphine | 10 |
| Bendamustine | 30 | Mycophenolic acid | 40 |
| Bosutinib | 100 | Nelfinavir | 30 |
| Cefepime | 500 | Nevirapine | 30 |
| Ceftazidime | 500 | Olanzapine | 10 |
| Ciprofloxacin | 100 | Penicillin V | 100 |
| Citalopram | 10 | Piperacillin | 500 |
| Clonazepam | 10 | Posaconazole | 20 |
| Codeine | 10 | Prednisolone | 200 |
| Colistimethate sodium | 100 | Ritonavir | 30 |
| Cyclosporin A | 40 | Sirolimus | 10 |
| Darunavir | 30 | Stavudine | 30 |
| Dasatinib | 100 | Tazobactam | 100 |
| Efavirenz | 30 | Tacrolimus | 10 |
| Emtricitabine | 30 | Tenofovir | 30 |
| Erythromycin | 200 | Tipranavir | 30 |
| Fluconazole | 30 | Tobramycin | 100 |
| Fosamprenavir | 30 | Trimethoprim | 50 |
| Gabapentin | 100 | Sulfamethoxazole | 400 |
| Gentamicin | 100 | Vancomycin | 250 |
| Itraconazole | 20 | Vincristine | 100 |
| Lamivudine | 30 | Zolpidem | 30 |

13 REFERENCES

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14 TRADEMARKS

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