# QMS® Everolimus (EVER)

thermo scientific

**IVD** **For In Vitro Diagnostic Use Only**

**REF** **0373852**

This Quantitative Microsphere System (QMS) package insert must be read carefully prior to use. Package insert instructions must be followed accordingly. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

## Intended Use

The QMS® Everolimus assay is to be used for the quantitative determination of everolimus in human whole blood on automated clinical chemistry analyzers.

The QMS Everolimus assay is intended to be used as an aid in the management of patients receiving everolimus therapy for those organ transplant procedures indicated in the chart for each specific country. The chart below indicates by an "X" where market approval for the drug has been granted for the given transplant type.

| Country | Transplant Type | | | Country | Transplant Type | | |
|---|---|---|---|---|---|---|---|
| | Kidney | Heart | Liver | | Kidney | Heart | Liver |
| Argentina | X | X | X | Lebanon | X | X | X |
| Australia | X | X | | Lithuania | X | X | X |
| Austria | X | X | X | Luxemburg | X | X | X |
| Bahrain | X | X | X | Malaysia | X | X | |
| Belgium | X | X | X | Malta | X | X | X |
| Brazil | X | X | X | Netherlands | X | X | X |
| Bulgaria | X | X | X | New Zealand | X | X | X |
| Canada | X | | | Norway | X | X | X |
| Chile | X | X | X | Oman | X | X | X |
| Colombia | X | X | | Peru | X | X | |
| Costa Rica | X | X | X | Philippines | X | X | X |
| Cyprus | X | X | X | Poland | X | X | X |
| Czech Republic | X | X | X | Portugal | X | X | X |
| Denmark | X | X | X | Qatar | X | X | |
| Dominican Republic | X | X | | Romania | X | X | X |
| Ecuador | X | X | | Russia | X | X | |
| Egypt | X | X | X | Saudi Arabia | X | X | X |
| Estonia | X | X | X | Singapore | X | X | X |
| Finland | X | X | X | Slovakia | X | X | X |
| France | X | X | X | Slovenia | X | X | X |
| Germany | X | X | X | South Africa | X | X | X |
| Greece | X | X | X | South Korea | X | X | X |
| Hong Kong | X | X | X | Spain | X | X | X |
| Hungary | X | X | X | Sweden | X | X | X |
| Iceland | X | X | X | Switzerland | X | X | X |
| India | X | X | | Taiwan | X | X | X |
| Italy | X | X | X | Thailand | X | X | X |
| Jordan | X | X | | Turkey | X | X | X |
| Kuwait | X | X | | Venezuela | X | X | |
| Latvia | X | X | X | | | | |

## Summary and Explanation of the Test

Everolimus is a macrolide immunosuppressant derived by chemical modification of the natural product rapamycin. Rapamycin is produced by certain strains of Streptomyces hygroscopicus.[1]

Immunosupressive treatment strategies are aimed at prevention of T cell activation and/or proliferation. Everolimus acts as a proliferation inhibitor. On a cellular level everolimus inhibits, in general, growth factor-stimulated cell proliferation irrespective of the cell lineage or growth factor involved. Inhibition is reversible since everolimus is not a cytotoxic compound. Everolimus inhibits the T cell response to growth factors arresting clonal expansion of activated T cells by inhibiting G1 to S phase.[3] Calcineurin inhibitors, cyclosporine (CsA) and tacrolimus, prevent the activation of T cells by inhibiting G0 to G1 phase transition. The different modes of action for everolimus and calcineurin inhibitors such as cyclosporine provide adequate rationale for the pharmacodynamic synergy.[1-3]

Monitoring blood everolimus concentrations is recommended as an aid in patient management with the clinical use of everolimus.[4,5] The preferred matrix is whole blood because, at therapeutic concentrations, the compound is predominately partitioned into erythrocytes. Liquid chromatography coupled to mass spectrometry has been used to measure the concentration of everolimus in blood.[6-8]

## Principles of the Procedure

The QMS Everolimus assay is a homogeneous particle-enhanced turbidimetric immunoassay. The assay is based on competition between drug in the sample and drug coated onto a microparticle for antibody binding sites of the everolimus antibody reagent. The everolimus-coated microparticle reagent is rapidly agglutinated in the presence of the anti-everolimus antibody reagent and in the absence of any competing drug in the sample. The rate of absorbance change is measured photometrically. When a sample containing everolimus is added, the agglutination reaction is partially inhibited, slowing down the rate of absorbance change. A concentration-dependent classic agglutination inhibition curve can be obtained with maximum rate of agglutination at the lowest everolimus concentration and the lowest agglutination rate at the highest everolimus concentration.

## Reagents

QMS Everolimus is supplied as a liquid, ready-to-use, three-reagent kit that contains:

| | | |
|---|---|---|
| **REF** | 0373852 | |
| | Reagent 1 | 1 x 22 mL |
| | Reagent 2 | 1 x 8 mL |
| **PRE** | Precipitation Reagent | 1 x 8 mL |

***Materials Required but not Provided***

| REF | Kit Description |
|---|---|
| 0373860 | QMS Everolimus Calibrators CAL A-F: 1 x 3.0 mL |
| 0373878 | QMS Everolimus Controls Levels 1-3: 1 x 3.0 mL |
| | Methanol (HPLC grade) |

***Reactive Ingredients***

| INGRED | Ingredient | Concentration |
|---|---|---|
| Reagent 1 | IgM Antisera (Goat) | ≤3.5% |
| | Human Serum Albumin (HSA) | ≤1.0% |
| | Anti-Everolimus Polyclonal Antibody (Rabbit) | <1.0% |
| | Sodium Azide | ≤0.09% |
| Reagent 2 | Everolimus-coated Microparticles | <0.6% |
| | Sodium Azide | ≤0.09% |
| PRE | Copper (II) Sulfate | ≤6.4% |
| | Sodium Azide | ≤0.09% |

## Reagent Handling and Storage

- Reagent 1, Reagent 2, and **PRE** Ready for Use
- Before use, invert several times, avoiding the formation of bubbles.
- Remove air bubbles, if present in the reagent cartridge, with a new applicator stick. Alternatively, allow the reagent to sit at the appropriate storage temperature to allow the bubbles to dissipate. To minimize volume depletion, do not use a transfer pipette to remove the bubbles.
- When either the Reagent 1 or Reagent 2 cartridge becomes empty, replace both cartridges and verify calibration with at least two levels of controls according to the established Quality Control requirements for your laboratory. If control results fall outside acceptable ranges, recalibration may be necessary.
- Refer to the analyzer specific Assay System Parameter sheet for system specific information.
- In the case of accidental spill, clean and dispose of material according to your laboratory's SOP, local, and state regulations.
- In the case of damaged packaging on arrival, contact your technical support representative (refer to back page of this PI).

⚠ **CAUTION:** Reagent bubbles may interfere with proper detection of reagent level in the cartridge, causing insufficient reagent aspiration that could impact results.

2°C 8°C The unopened reagents are stable until the expiration date when stored at 2 to 8°C. **Do not freeze reagents or expose them to temperatures above 32°C.**

Light may affect Reagent 2 stability. Keep stored reagents out of light.

## ⚠ Warnings and Precautions

For in vitro diagnostic use. Do not mix materials from different kit lot numbers. Avoid the use of short drawn samples. Increased amounts of anticoagulant may produce erroneous results.

**CAUTION:** This product contains human sourced and/or potentially infectious components. Components sourced from human blood have been tested by FDA-approved methods and found to be nonreactive for HBsAg, anti-HIV 1/2, and anti-HCV. No known test method can offer complete assurance that products derived from human sources or inactivated microorganisms will not transmit infection. Therefore, it is recommended that all human sourced materials be considered potentially infectious and handled with appropriate biosafety practices.

**DANGER:** QMS Everolimus Reagent 1 contains ≤3.5% IgM Antisera (Goat) serum and ≤1.0% Rabbit Polyclonal Antibody.
H317 - May cause allergic skin reaction.
H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled.

Avoid breathing mist or vapor. Contaminated work clothing should not be allowed out of the workplace. Wear protective gloves/eye protection/face protection. In case of inadequate ventilation wear respiratory protection. If on skin: Wash with plenty of soap and water. IF INHALED: If breathing is difficult, remove victim to fresh air and keep at rest in a position comfortable for breathing. If skin irritation or rash occurs: Get medical advice/attention. If experiencing respiratory symptoms: Call a POISON CENTER or doctor/physician. Wash contaminated clothing before reuse. Dispose of contents/container to location in accordance with local/regional/national/international regulations.

**WARNING:** QMS Everolimus PRE contains ≤6.4% Copper (II) sulfate and ≤0.09% Sodium azide.
H400 - Very toxic to aquatic life.
H410 - Very toxic to aquatic life with long-lasting effects.

Avoid release to the environment. Collect spillage. Dispose of contents/container to location in accordance with local/regional/national/international regulations.

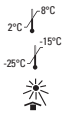
Reagents used in the assay components contain ≤0.09% sodium azide. Avoid contact with skin and mucous membranes. Refer to SDS for additional precautions, handling instructions, and accidental exposure treatment.

## Specimen Collection and Handling

The following specimen collection tubes may be used for the QMS Everolimus assay:

| | Glass | Plastic |
|---|---|---|
| **Whole Blood** | EDTA ($K_3$) | EDTA ($K_2$) |

Other specimen collection tubes have not been validated for use with the QMS Everolimus assay. Follow the manufacturer's processing instructions for all collection tubes.




The use of short drawn samples may yield erroneous results. Specimens may be stored up to 3 days at 2 to 8°C. If testing will be delayed more than 3 days, specimens should be stored frozen (-20 ± 5°C) up to 28 days prior to being tested. Light may affect sample stability. Keep stored samples out of light. Samples for the QMS Everolimus assay should be drawn just prior to a dose (trough level), to confirm that an adequate dose has been prescribed. The trough concentration is most indicative of the therapeutic level of everolimus.[2]

## Procedure

***Extraction Procedure for Samples, Calibrators, and Controls***

Extracts must be run immediately after extraction.

1. Prepare micro-centrifuge tubes for extraction of samples, calibrators and controls.
2. Calibrators, controls and samples should be thawed completely and brought to room temperature before extraction. Mix samples, calibrators and controls well by inversion.
3. Accurately pipette 300 µL of each calibrator, control, or sample to be assayed into the appropriate micro-centrifuge tube.
4. Accurately dispense 350 µL of methanol into each micro-centrifuge tube.
5. Accurately pipette 50 µL of QMS Everolimus Precipitation reagent into each micro-centrifuge tube.
6. Cap each micro-centrifuge tube immediately to prevent evaporation, then vigorously mix/vortex at the highest speed for at least 35 seconds. Note: it may be necessary to invert the tube and remix to ensure complete mixing. After mixing, the sample color should change from red to brown.
7. Place the tubes in a micro-centrifuge and centrifuge for at least 8 minutes at 13,400 x g.
8. After centrifuging, decant the supernatant into appropriate sample cups. Avoid transferring particulates and bubbles. Load cups on to the instrument.
9. Begin the analyzer calibration or assay process immediately to minimize sample evaporation.
10. Dispose of extracts after analysis. Retesting of samples requires fresh extractions.

## Barcode Usage

Reagent labels have a dedicated system barcode that most analyzers will ignore if unrecognized. If the analyzer returns an error code, overlay the barcode with solid-colored tape. Contact Technical Services for assistance if needed.

## Assay Procedure

The assay is performed at a wavelength of 700 nm. For a detailed description of how to run and calibrate an assay, refer to the instrument-specific operations manual.

## Specimen Dilution Procedure

Use QMS Everolimus CAL A (0.0 ng/mL) to manually dilute samples outside the linearity of the assay.

## Manual Dilution Protocol

A manual dilution can be performed on patient samples with everolimus concentrations reported as greater than 20 ng/mL by making a 1:1 dilution of the specimen with QMS Everolimus CAL A (0.0 ng/mL) before extracting the sample. The dilution must be performed so the diluted test result reads greater than the assay sensitivity of 1.5 ng/mL. The concentration reported must be multiplied by the manual dilution factor to obtain the final sample concentration.

$$\text{Final Sample Concentration} = \text{Reported Concentration} \times \text{Manual Dilution Factor}$$

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

## Calibration

The QMS Everolimus assay must be calibrated using a full calibration (6-point) procedure. To perform a full calibration, test the QMS Everolimus Calibrators A,B,C,D,E, and F in duplicate. Calibration is required with each new lot number. Verify the calibration curve with at least two levels of controls according to the established Quality Control requirements for your laboratory. If control results fall outside acceptable ranges, correction action should be taken.

Note: Everolimus CAL A is the calibration blank for this assay.

## Quality Control

As appropriate, refer to your laboratory Standard Operating Procedure(s) and/or Quality Assurance Plan for additional quality control requirements and potential corrective actions. All quality control requirements should be performed in conformance with local, state, and/or government regulations or accreditation requirements. Each laboratory should establish its own control ranges and calibration frequency.

***Recommended control requirements for the QMS Everolimus assay:***

- A minimum of two levels of controls spanning the medical decision range should be run as frequently as needed to control for extraction batches.
- If more frequent control monitoring is required, follow the established Quality Control procedures for your laboratory.
- If quality control results do not fall within an acceptable range defined by your laboratory, patient values may be suspect and corrective action should be taken.

## Results

The result units for the QMS Everolimus assay are reported as ng/mL.

As with all analyte determinations, the everolimus value should be used in conjunction with information available from clinical evaluations and other diagnostic procedures

***Result Error Codes***

Some results may contain Result Error Codes. Refer to the instrument-specific operations manual for a description of the error codes.

## Limitations Of The Procedure

The QMS Everolimus assay has been designed to only recover clinical patient samples accurately and not artificially spiked samples.

Only QMS Everolimus Calibrators and Controls should be used with the QMS Everolimus assay. Accurate quantitative determination of everolimus cannot be obtained if the QMS Everolimus Calibrators set REF (0373860) is not used in calibration of the QMS Everoilmus assay.

The assay should not be used on patients who have recently been administered sirolimus (until sirolimus parent compound and metabolites are fully cleared) since the assay cross-reacts with sirolimus and its metabolites.

Interfering heterophile antibodies occur at a low frequency in the general population. In rare cases patient samples may contain heterophile antibodies. These antibodies can cause autoagglutination of the microparticle reagent leading to undetected erroneously low results.

For diagnostic purposes, the test findings should always be assessed in conjunction with the patient's medical history, clinical examinations and other findings.

See the Specimen Collection and Handling and Specific Performance Characteristics sections of this package insert.

## Expected Values

A general therapeutic range for everolimus in whole blood is 3-8 ng/mL. The complexity of the clinical state, individual differences in sensitivity to immunosuppressive and nephrotoxic effects of everolimus, coadministration of other immunosuppressants, type of transplant, time post-transplant, and a number of other factors contribute to different requirements for optimal blood levels of everolimus. Therefore, individual everolimus values cannot be used as the sole indicator for making changes in treatment regimen and each patient should be thoroughly evaluated clinically before changes in treatment regimen are made. Each user must establish ranges based on clinical experience. Therapeutic ranges vary accordingly to the method used and therefore should be established for each method. Values obtained with different methods cannot be used interchangeably due to differences in methods and cross-reactivity with metabolites, nor should correction factors be applied. Therefore, consistent use of one assay for individual patients is recommended. Optimal dose adjustment should be based on more than a single trough sample.

## Specific Performance Characteristics

Representative performance results obtained on a commercially available automated clinical chemistry analyzer that employs turbidimetric quantitative analysis are shown below.

Disclaimer: Not all organ transplant populations have been validated in all regulatory regions. Refer to the table in Intended Use section for country-specific uses.

***Sensitivity***

The limit of quantitation (LOQ) of the QMS Everolimus assay is defined as the lowest concentration for which acceptable inter-assay precision and recovery is observed (often considered ≤20% CV with ±15% recovery). The LOQ was determined to be 1.3 ng/mL.

***Assay Range***
The range of the assay is 1.5 to 20 ng/mL.

***Accuracy***
Linearity studies were performed by diluting a high patient sample to concentrations across the assay range. The dilutions were made with whole blood hemolysate. Linearity at specific dilutions were considered acceptable if the percent recovery was 100 ± 10.

## Linearity

| Theoretical Concentration (ng/mL) | Avg. of 12 Reps | % CV | % Recovery |
|---|---|---|---|
| 0.00 | 0.33 | - | 0.00 |
| 1.12 | 1.29 | 17.28 | 114.70 |
| 2.23 | 2.36 | 8.36 | 105.17 |
| 4.46 | 4.34 | 5.25 | 96.53 |
| 6.70 | 6.24 | 3.03 | 92.51 |
| 8.93 | 8.60 | 2.55 | 95.64 |
| 11.16 | 11.14 | 3.72 | 99.11 |
| 13.39 | 13.21 | 2.63 | 97.94 |
| 15.63 | 15.85 | 3.17 | 100.72 |
| 17.86 | 17.88 | 6.73 | 99.42 |
| 20.09 | 19.88 | 3.83 | 98.24 |
| 22.48 | 22.32 | 7.82 | 99.30 |

## Method Comparison
A correlation study was performed using 150 kidney transplant patient samples. Results from the QMS Everolimus assay were compared with results from LC/MS. Results of the Passing-Bablok[9] regression analysis for the study are shown below.

| | |
|---|---|
| Slope | 1.11 |
| Y-Intercept | -0.005 |
| Correlation Coefficient (R) | 0.96 |
| Number of Samples | 150 |

A second correlation study was done using 41 heart transplant patient samples. The QMS Everolimus assay results were compared with the LC/MS results. The results of the Passing-Bablok regression analysis are shown below.

| | |
|---|---|
| Slope | 1.00 |
| Y-Intercept | -0.15 |
| Correlation Coefficient (R) | 0.96 |
| Number of Samples | 41 |

A third correlation study was done using 111 liver transplant patient samples. The QMS Everolimus assay results were compared with the LC/MS results. The results of the Passing-Bablok regression analysis are shown below.

| | |
|---|---|
| Slope | 0.98 |
| Y-Intercept | -0.06 |
| Correlation Coefficient (R) | 0.93 |
| Number of Samples | 111 |

## Precision
Precision was determined as described in NCCLS protocol EP5-A2.[10]

A tri-level human blood based control containing everolimus and a tri-level patient sample pool was used in the study. Each level was assayed in duplicate twice a day for 20 days. Each of the runs per day was separated by at least two hours. The means, the between day, within run and total SD and CV (%) were calculated. Representative results are shown below.

| | | | Within Run | | Between Day | | Total | |
|---|---|---|---|---|---|---|---|---|
| Control | N | Mean (ng/mL) | SD | CV (%) | SD | CV (%) | SD | CV (%) |
| 1 | 80 | 3.93 | 0.13 | 3.21 | 0.22 | 5.65 | 0.28 | 7.19 |
| 2 | 80 | 8.20 | 0.25 | 3.01 | 0.33 | 4.05 | 0.51 | 6.16 |
| 3 | 80 | 14.90 | 0.83 | 5.57 | 0.68 | 4.55 | 1.11 | 7.47 |
| **Patient Pools** | | | | | | | | |
| 1 | 80 | 3.87 | 0.28 | 7.31 | 0.18 | 4.59 | 0.37 | 9.45 |
| 2 | 80 | 8.73 | 0.18 | 2.11 | 0.46 | 5.24 | 0.64 | 7.27 |
| 3 | 80 | 12.07 | 0.43 | 3.59 | 0.32 | 2.67 | 0.80 | 6.62 |

## Interfering Substances
***Specificity***
Interference studies were conducted using NCCLS protocol EP7-A as a guideline.[11,12] Cross-reactivity was tested for the available major metabolites of everolimus. Other medications routinely administered with everolimus and endogenous substances were also tested to determine whether these compounds affect the quantitation of everolimus concentrations using the QMS Everolimus assay.

***Metabolites***
Studies were conducted to examine the cross-reactivity of the QMS Everolimus antiserum to major everolimus metabolites. The compounds tested were added in two concentrations to human blood hemolysate containing 5 ng/mL of everolimus drug and tested using the QMS Everolimus assay. Percent cross-reactivity was calculated. The results are shown below:

| Compound Tested | Concentration Tested (ng/mL) | Recovered Concentration (ng/mL) | % Cross-Reactivity |
|---|---|---|---|
| RAD SA | 5 | 6.08 | 7 |
| RAD SA | 20 | 6.07 | 2 |
| RAD PSA | 5 | 6.33 | 12 |
| RAD PSA | 20 | 9.00 | 16 |
| RAD PC | 5 | 8.86 | 63 |
| RAD PC | 20 | 17.61 | 59 |
| 45/46 OH RAD | 5 | 5.82 | ND |
| 45/46 OH RAD | 20 | 6.13 | 2 |
| 24 OH RAD | 5 | 6.23 | 9 |
| 24 OH RAD | 20 | 6.81 | 5 |
| 25 OH RAD | 5 | 6.56 | 15 |
| 25 OH RAD | 20 | 10.24 | 22 |

ND = Not Detected

In addition, studies were conducted to examine the cross-reactivity of the QMS Everolimus antiserum to sirolimus and its major metabolites. The compounds tested were added to the human blood hemolysate containing 5.5 ng/mL of everolimus drug and tested using the QMS Everolimus assay. Percent cross-reactivity was calculated. The results are shown below.

| Sirolimus and Sirolimus Metabolites | | | |
|---|---|---|---|
| **Compound Tested** | **Concentration Tested (ng/mL)** | **Recovered Concentration (ng/mL)** | **% Cross-Reactivity** |
| Sirolimus | 10 | 9.94 | 46 |
| Trihydroxy-sirolimus; 7,41-O-didesmethyl sirolimus | 90 | 9.34 | 4 |
| 41-O-desmethyl-hydroxy sirolimus | 90 | 8.55 | 3 |
| 41-O-desmethyl-hydroxy sirolimus; 7-O-desmethyl sirolimus | 90 | 7.29 | 2 |
| 11-hydroxy sirolimus | 90 | 16.43 | 12 |
| Isomer of 11-hydroxy sirolimus | 90 | 11.00 | 6 |
| Hydroxy sirolimus | 90 | 6.96 | 2 |
| N-oxide sirolimus | 90 | 12.10 | 7 |
| Isomer of hydroxyl sirolimus or N-oxide sirolimus | 90 | 6.71 | 1 |
| 41-O-desmethyl sirolimus; 32-O-desmethyl sirolimus | 30 | 18.32 | 45 |

**Endogenous Substances**

The following compounds, when tested with the QMS Everolimus assay at the concentrations indicated, resulted in less than 10% error in detecting everolimus. The results are shown below.

| Interfering Substance | Interferent Concentration | N | Everolimus (ng/mL) | % Recovery |
|---|---|---|---|---|
| Bilirubin | 60 mg/dL | 10 | 4.45 | 95.86 |
| Cholesterol | 347 mg/dL | 3 | 4.22 | 101.10 |
| Creatinine | 5 mg/dL | 3 | 5.40 | 99.60 |
| Gamma Globulin | 12 g/dL | 3 | 4.06 | 92.86 |
| HAMA type 1* | Normal Human Level | 3 | 4.22 | 102.92 |
| HAMA type 2* | Normal Human Level | 3 | 4.22 | 95.02 |
| Hematocrit | 60% | 10 | 4.18 | 101.89 |
| Rheumatoid Factor | 1350 IU | 3 | 4.22 | 101.42 |
| Total Protein | 12 g/dL | 3 | 4.06 | 105.17 |
| Triglyceride | 1500 mg/dL | 3 | 4.22 | 100.60 |
| Uric Acid | 40 mg/dL | 3 | 4.22 | 99.53 |

*HAMA = human anti-mouse antibodies

**Drug Cross-Reactivity**

Cross-reactivity was tested with drugs that are routinely administered with everolimus. Cross-reactants were analyzed in an everolimus-spiked hemolysate at 5-6 ng/mL. The following compounds were tested.

| Compound | Concentration Tested µg/mL | % Cross-Reactivity |
|---|---|---|
| Acetaminophen | 200 | ND |
| N-Acetylprocainamide | 120 | ND |
| Acyclovir | 1000 | 0.0 |
| Albuterol | 0.18 | ND |
| Allopurinol | 60 | ND |
| Amikacin | 150 | 0.0 |
| Amphotericin B | 100 | 0.0 |
| Ascorbic Acid | 30 | ND |
| Atenolol | 40 | ND |
| Azothioprene | 10 | ND |
| Bactrim (5:1 Sulfamethoxazole: Trimethoprim) | 525 Sulfamethoxazole 45 Trimethoprim | 0.0 |
| Caffeine | 100 | ND |
| Captopril | 50 | 0.0 |
| Carbamazepine | 120 | 0.0 |
| Cefaclor | 230 | ND |
| Chloramphenicol | 250 | ND |
| Cimetidine | 100 | ND |
| Ciprofloxacin | 250 | 0.0 |
| Cyclosporin A | 1 | ND |
| Digoxin | 0.01 | -2.0 |
| Disopyramide | 30 | 0.0 |
| Erythromycin | 200 | 0.0 |
| Ethanol | 3500 | ND |
| Fluconazole | 75 | 0.0 |
| Flucytosine | 300 | 0.0 |
| Folic Acid | 0.01 | ND |
| Furosemide | 100 | ND |
| Ganciclovir | 1000 | ND |
| Gemfibrozil | 75 | ND |
| Gentamicin | 20 | ND |
| Glipizide | 60 | ND |

Table con't

| Compound | Concentration Tested µg/mL | % Cross-Reactivity |
|---|---|---|
| Glyburide | 40 | ND |
| Heparin | 16 | 0.0 |
| Hydralazine | 32 | ND |
| Hydrochlorothiazide | 40 | ND |
| Ibuprofen | 400 | ND |
| Insulin | 0.0167 | 1.0 |
| Intralipid | 15000 | ND |
| Isoniazid | 70 | ND |
| Isoproterenol HCl | 0.06 | ND |
| Itraconazole | 17 | ND |
| Kanamycin A | 100 | ND |
| Kanamycin B | 100 | ND |
| Ketoconazole | 10 | ND |
| Labetalol | 200 | ND |
| Lidocaine | 100 | ND |
| Lithium | 22.2 | ND |
| Lovastatin | 4 | 0.0 |
| Metformin HCl | 5100 | ND |
| Methicillin | 240 | ND |
| Methotrexate | 910 | ND |
| Metoclopramide | 4 | ND |
| Misoprostol | 0.015 | ND |
| Morphine Sulfate | 6 | ND |
| Mycophenolic Acid | 250 | ND |
| Nadolol | 333 | ND |
| Naproxen | 1000 | 0.0 |
| Niacin | 800 | ND |
| Nifedipine | 120 | 0.0 |
| Omeprazole | 14 | ND |
| Pantoprazole sodium | 15 | 0.0 |
| Penicillin G | 100 | 0.0 |
| Phenobarbital | 150 | ND |
| Phenytoin | 100 | 0.0 |
| Piperacillin | 8 | ND |
| Prazosin | 25 | ND |
| Prednisone | 12 | ND |
| Prednisolone | 12 | ND |
| Primidone | 100 | 0.0 |
| Procainamide | 25 | ND |
| Propanolol | 0.5 | ND |
| Quinidine | 100 | ND |
| Ranitidine | 200 | ND |
| Rifampin | 50 | 0.0 |
| Salicyclic Acid | 500 | ND |
| Sotrastaurin | 40 | 0.0 |
| Spectinomycin | 100 | ND |
| Sulfamethoxazole | 400 | 0.0 |
| Tacrolimus | 0.04 | 1.0 |
| Theophylline | 250 | ND |
| Tobramycin | 20 | ND |

Table con't

| Compound | Concentration Tested µg/mL | % Cross-Reactivity |
|---|---|---|
| Triamterene | 600 | 0.0 |
| Trimethoprim | 20 | ND |
| Valganciclovir HCl | 36 | 0.0 |
| Valproic Acid | 1000 | 0.0 |
| Vancomycin | 630 | ND |
| Verapamil | 10 | ND |

ND = Not Detectable. The cross-reactivity is considered not detectable if the difference between the spiked sample and the control is less than the standard deviation of the control replicates.

**Reference**


1. Certican (Everolimus) dispersible tablets proposed labeling. Novartis NDA No. 21-561 and 26-628. December 19, 2002.
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