Immunosuppressants in whole blood

4180 P IMM

Instructions for use, LC-MS/MS assay

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Contents

1. General Information

1.1 Information for the Device

4180 P IMM - Immunosuppressants Reagent Set
UDI-DI: 8720514311790

For information on the individual components of this set, refer to chapter 2 of these instructions for use.

1.2 Intended Purpose

This Immunosuppressants kit is intended for the determination of four (4) immunosuppressant medications in whole blood, conducted by laboratory professionals on LC-MS/MS.

1.2.1 Measurands

Cyclosporin A

Everolimus

Sirolimus
Rapamycin

Tacrolimus

1.2.2 Function

The function of this device is to aid in the monitoring of several immunosuppressant medications, refer to paragraph 1.2.1, by the assessment of medicine levels by determination of these levels of immunosuppressants in whole blood, performed by automated quantitative LC-MS/MS assay technology.

1.2.3 Specific Information indented to be provided

Deviant measurand values can be an indication of the following physiological or pathological states and/or conditions:

Incorrect dose/use of specified immunosuppressant medication.

1.2.5 Required Specimen

Human whole blood.

1.2.5.1 Conditions for collection, handling and preparation of specimen

Use EDTA-tubes to collect the specimens. Store at 2-8 °C.[1] [2] [3] [4]

1.2.6 Testing Population

Patients known or suspected to be using one of the measured immunosuppressants specified under paragraph 1.2.1.

1.3 Intended User

Laboratory Professional Use.

1.4 Test Principle

In this analytical method, 4 immunosuppressants are determined from human whole blood by (U)HPLC LC-MS/MS. Prior to the LC-MS/MS analysis, a sample clean-up is performed to remove the sample matrix and to spike the samples with the internal standard. The prepared samples are injected into the UHPLC system and, after separation by chromatography on an analytical C-18 column, the compounds are ionized by electrospray ionization (ESI) and detected by MS/MS.

1.5 Clinical Background

Patients who receive a solid organ transplantation (SOT) or a stem cell transplantation (SCT) require immunosuppressant drugs to suppress the patients' immune response to the transplant and prevent rejection of the transplant. The goal with immunosuppression is to induce donor specific tolerance for the transplant with minimal impairing of the patients' defenses or increasing the susceptibility to infections. The most common immunosuppressants prescribed are the calcineurine inhibitors cyclosporine and tacrolimus, and the mTOR inhibitors sirolimus and everolimus. These immunosuppressants are used for the prophylaxis and treatment of graft rejection following SOT (kidney, lung, hart, and liver) and SCT [5,6].

With cyclosporine, tacrolimus, sirolimus, and everolimus, clinical variability due to inter- and intra- patient pharmacokinetic variability is seen. This pharmacokinetic variability, in combination with an excellent correlation between blood concentrations and efficacy/toxicity of the treatment and the narrow therapeutic range of the immunosuppressive drugs, makes monitoring of blood concentrations a crucial part of the treatment. The therapeutic range for each immunosuppressant drug depends on post-transplant time, concomitant immunosuppressive medication, and immunological risk[7].

[1] https://tdm-monografie.org/ciclosporine/
[2] https://tdm-monografie.org/everolimus/
[3] https://tdm-monografie.org/sirolimus/
[4] https://tdm-monografie.org/tacrolimus/
[5] Allison. Immunosuppressive Therapy in Transplantation. Nurs Clin North Am. 2016;51(1):107-20
[6] Medication Guidelines for Solid Organ Transplants, BC Transplant Society, Canada 2021
[7] Brunet et al. Therapeutic Drug Monitoring of Tacrolimus-Personalized Therapy: Second Consensus Report. Ther Drug Monit 2019;41(3):261-307

Therapeutic Drug Monitoring (TDM) to optimize immunosuppressive treatment and minimizing drug-related toxicity is therefore standard care in the clinical setting as well as in the outpatient setting, and TDM is advised in the Summary of Product Characteristics (SPC) of cyclosporine, tacrolimus, sirolimus, and everolimus[8,9,10,11]. Furthermore, a number of consensus documents on TDM of immunosuppressive drugs have been written to assist pharmacists and clinicians to individualize the treatment[3,12].

Besides standard monitoring of drug concentrations, extra monitoring is recommended to ensure that an appropriate systemic drug exposure is maintained in case of clinical treatment failure (the occurrence of an acute rejection episode), dose adjustments or changes in the immunosuppressive regimen, a switch in (generic) formulation of the immunosuppressive drug, suspected problems with the absorption of the drug, adverse events, drug-drug interactions, relevant comorbidities, and if nonadherence is suspected[3,4,5,6,7,8,13].

The Diagnotix kit for measuring immunosuppressive drugs includes cyclosporine, tacrolimus, sirolimus, and everolimus. For all these drugs, reference concentrations are based on literature and an overview of target concentrations can be found in several articles as well in the SPC of cyclosporine, tacrolimus, sirolimus, and everolimus[3,4,5,6,7,8,9,14,15,16,17,18].

In conclusion, immunosuppressive drugs fulfill the prerequisites for TDM, having a narrow therapeutic window, a high intra- and inter-individual pharmacokinetic variability, and an established exposure-response relationship. TDM of immunosuppressive drugs is recommended for optimal use of these drugs in clinical practice as stated in the SPC of these drugs as well as in several international guidelines and consensus documents.

1.6 Notice Regarding Serious Incidents

Following (EU) 2017/746 Annex I, Chapter III, 20.4.1 af), any serious incident that has occurred in relation to this device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

[8] Summary of product characteristics Prograft Available via: https://www.ema.europa.eu
[9] Summary of product characteristics Certican Available via: https://www.ema.europa.eu
[10] Summary of product characteristics Rapamunde Available via: https://www.ema.europa.eu
[11] Summary of product characteristics Neoral Available via: https://www.ema.europa.eu
[12] Shipkova et al. Therapeutic Drug Monitoring of Everolimus: A Consensus Report. Therapeutic Drug Monitoring. 2016;38(2):143-69
[13] van Gelder. European Society for Organ Transplantation Advisory Committee recommendations on generic substitution of immunosuppressive drugs. Practice Guideline Transpl Int 2011;24(12):1135-41
[14] Rodríguez-Perálvarez et al. Tacrolimus trough levels, rejection and renal impairment in liver transplantation: a systematic review and meta-analysis. Am J Transplant. 2012;12(10):2797–814
[15] Moes et al. Sirolimus and everolimus in kidney transplantation. Drug Discov Today. 2015;20(10):1243-9
[16] Kahan et al. Therapeutic drug monitoring of sirolimus: correlations with efficacy and toxicity. Clin Transplant 2000;14(2):97-109
[17] Diciolla et al. C2 and C0 values for monitoring cyclosporine therapy in stable heart transplant recipients. Transplantation Proceedings 2005;37:1355-1359
[18] Andrews et al. Cyclosporin: revisions in monitoring guidelines and review of current analytical methods. Ann Clin Biochem. 2002;39:424-35

2. Components and Accessories

2.1 Description of Components

All components are for LC-MS/MS use only, components also may contain other ingredients than those listed as active ingredients below which might influence the measurement. All declared stabilities are only valid in case of no bacterial contamination.

2.1.1 Calibrators and Controls

4181 CAL P IMM | Immunosuppressants Calibrator Set
UDI: 8720514311103

A six-point lyophilized whole blood calibrator at clinically relevant levels, refer to the value data sheet provided with each set for specific values per production batch.

4182 CON P IMM | Immunosuppressants Control Set
UDI: 8720514311110

4193 P IMM | Immunosuppressants Control I
UDI: 8720514311226
4194 P IMM | Immunosuppressants Control II
UDI: 8720514311233
4195 P IMM | Immunosuppressants Control III
UDI: 8720514311240

Three levels of lyophilized whole blood controls at clinically relevant levels for quality control purposes, refer to the value data sheet provided with each set for specific values per production batch.

2.1.1.1 Handling

Reconstitute the calibrators and controls as follows:

1. Carefully remove the cap and rubber plug avoiding any loss of contents.
2. Reconstitute Immunosuppressants Calibrator Set and Controls with exactly 500 µl distilled or deionised water using a volumetric pipette.
   Note: Diagnotix strongly recommends the use of type 1 ultrapure (LC-MS grade) water.
3. Re-place the plug and let stand during 15 minutes.
4. Swirl the vial carefully and mix thoroughly making sure that all traces of dry material have dissolved, do not shake. Avoid foaming.
5. Let stand for 15 minutes at room temperature.
6. Swirl the vial carefully, do not shake. Avoid foaming.
7. Use the preparation as a patient sample.

2.1.1.2 Stability and Storage

The stability of the calibrators and controls are:

Before reconstitution:	2 - 8 °C	Until expiry date printed on the product label
After reconstitution:	-20 °C	4 weeks

2.1.1.3 Metrological Traceability

Metrological traceability is established by comparing each batch to the highest available order of reference material, as well as the last batch produced before the current batch.

For Immunosuppressants the highest available order of reference material has been established to be LGC Standards which is a division of LGC Group. This group is the designated National Measurement Institute for chemical and bioanalytical measurements in the United Kingdom.

Refer to the Value Data Sheet for this specific set for more information.

2.1.2 Deproteinization Solution + Internal Standard

4189 P IMM | Immunosuppressants Deproteinization Solution + Internal Standard
UDI: 8720514311189

An isotopic version of the measurand, dissolved in a deproteinization solution. Used to identify and correct potential deviating values, due to errors or varying circumstances in sample preparation or within the LC-MS/MS. The deproteinization solution furthermore deproteinizes the sample to prevent pollution in the LC-MS/MS.

Active ingredient(s): [$^{2}H_{12}$]-Cyclosporin A,
[$^{13}C_{2}$,$^{2}H_{4}$]-Everolimus,
[^{13}C,$^{2}H_{3}$]-Sirolimus
[^{13}C,$^{2}H_{4}$]-Tacrolimus.

Methanol 75% - <100%

2.1.2.1 Handling

The Reagent is liquid and ready for use.

2.1.2.2 Stability and Storage

The stability of the internal standard is:

Store at 2 - 8 °C. After first opening the Reagent can be used for 3 weeks if closed and stored at 2 - 8 °C.

2.1.3 Zinc Sulphate Solution

4190 P IMM | Immunosuppressants Zinc Sulphate Solution
UDI: 8720514311196

A solution provided to perform an extra pre-deproteinization step to prevent pollution in the LC-MS/MS.

Active ingredient(s): <1% Zinc Sulphate

2.1.3.1 Handling

The Reagent is liquid and ready for use.

2.1.3.2 Storage and Stability

Store at 2 - 8 °C. After first opening the Reagent can be used for 3 weeks if closed and stored at 2 - 8 °C.

2.1.4 Mobile Phases

4191 P IMM | Immunosuppressants Mobile Phase I
UDI: 8720514311202
4092 P IMM | Immunosuppressants Mobile Phase II
UDI: 8720514311219

Two mobile phases are provided to carry the sample through the LC-MS/MS. Different ratios of the mobile phases will allow different components to elute from the column at differing speeds.

Active ingredient(s):
Mobile Phase I: 2.5% -<10% Methanol
<1% Formic acid
Mobile Phase II: 75% - <100% Methanol
<1% Formic acid

2.1.4.1 Handling

The Reagents are liquid and ready for use.

2.1.4.2 Stability and storage

Store at 2 - 8 °C: After first opening the Reagent can be used for 6 weeks if closed and stored at 2 - 8 °C or 6 weeks on the UHPLC.

Store at RT: Diagnotix recommends storage at 2 - 8 °C, however before opening stability at room temperature is guaranteed for 3 months.

2.1.5 Autosampler Washing Solution

4196 P IMM | Immunosuppressants Autosampler washing solution
UDI: 8720514311806

A solution used to clean the UHPLC-MS/MS system after use, specifically designed to remove residue from testing the measurand.

Active ingredient(s): 75% - <100% Methanol

2.1.5.1 Handling

The Reagent is liquid and ready for use.

2.1.5.2 Stability and storage

Store at 2 - 8 °C. After first opening the Reagent can be used for 6 weeks if closed and stored at 2 - 8 °C or 2 weeks on the UHPLC.

2.2 List of components provided

4180 KIT P IMM - Complete Kit for immunosuppressants in whole blood

Contents (for 300 assays):

Immunosuppressants Calibrator Set (Calibrator 1 – 6)	4181 CAL P IMM	6 x 2 x 500 µl
Immunosuppressants Deproteinization Solution + Internal Standard	4189 P IMM	3 x 55 ml
Immunosuppressants Zinc Sulphate Solution	4190 P IMM	3 x 25 ml
Immunosuppressants Mobile Phase I	4191 P IMM	1 x 500 ml
Immunosuppressants Mobile Phase II	4192 P IMM	1 x 500 ml
Immunosuppressants Autosampler Washing Solution	4196 P IMM	1 x 1000 ml
Immunosuppressants Manual		

2.3 Separately available materials and components

Immunosuppressants Calibrator Set (Calibrator 1 – 6)	4181 CAL P IMM	6 x 2 x 500 µl
Immunosuppressants Deproteinization Solution + Internal Standard	4189 P IMM	3 x 55 ml
Immunosuppressants Zinc Sulphate Solution	4190 P IMM	3 x 25 ml
Immunosuppressants Mobile Phase I	4191 P IMM	1 x 500 ml
Immunosuppressants Mobile Phase II	4192 P IMM	1 x 500 ml
Immunosuppressants Autosampler Washing Solution	4196 P IMM	1 x 1000 ml

Analytical column Waters XBridge BEH C18 2,5µm 2,1x75mm XP	186006030	1 pc
Immunosuppressants Control I	4193 P IMM	10 x 500 µl
Immunosuppressants Control II	4194 P IMM	10 x 500 µl
Immunosuppressants Control III	4195 P IMM	10 x 500 µl
Immunosuppressants Control Set	4182 CON P IMM	3 x 3 x 500 µl

3. Warnings, precautions, measures and limitations of use

3.1 General

The device and its components must only be used in line with the intended purpose by the intended user as stated in chapter 1. Due to their nature, most reagents of this device contain or are largely composed of hazardous substances. Please refer to the Safety Data Sheets (SDS) for each of the components for specific hazards and measures to be taken.

Used components should be discarded and are not suitable for re-use.

3.1.1 Potentially infectious material

The human whole blood used for manufacturing calibrators and controls was tested for the following infectious markers and found negative: HIV1/2-, HBV- and HCV-antibodies, Hepatitis B-surface antigen, HIV1- and HCV-RNA, HBV-DNA (NAT). Nevertheless, the whole blood controls should be considered as potentially infectious and treated with appropriate care.

3.2 Interferences & Limitations

Visual evidence of lipemia, homolysis, or icterus (hyperbilirubinemia) and/or older age of the specimen may affect the performance of the device.

3.3 CMR substances

No CMR substances are used in any significant quantity in the manufacturing of this kit or its components.

3.4 Disposal

For the safe disposal of the components of this kit, please refer to the safety data sheet of the component in question.

4. Assay procedure

4.1 Settings and procedure

4.1.1 Required instruments and LC modules

Using this test kit requires a UHPLC system with tandem mass spectrometer (LC-MS/MS) with the following modules:

- Autosampler
- UHPLC gradient pump
- Column heater
- Degasser

4.2 The analytical system

4.2.1 Preparation of the analytical system

- Flush the LC system excluding the column.
- Set the UHPLC pump at a flow rate of 1 ml/min and flush the system for 10 minutes with Mobile Phase I and II (50 : 50).
- Connect the column with the column heater.
  (see arrow marking on the column)

After flushing the system, the equilibration is performed as follows:

- Set the UHPLC pump to a flow rate of 0.5 ml/min.
- Set the column heater to 30°C.
- Equilibrate the column for 15 minutes with Mobile Phase I.
- Start the program for the gradient and equilibrate for another 10 minutes.

4.2.2 Starting the analytical system

- Equilibrate the system.
- Check the temperature of the column.
- Initialize the injector.
- Start the programme on the LC-MS/MS system.

4.3 LC-MS/MS Parameters and Condition

Please note that the provided LC-MS/MS Parameters and Conditions are derived from the system used by Diagnotix to perform the validation of the analytical performance of this assay kit. Conditions may vary between LC-MS/MS, even between systems of the same type from the same manufacturer. End-user systems used to perform this assay may require optimization.

4.3.1 LC Parameters

UHPLC pump	Flow rate 0.5 ml/min
Mobile Phases I and II	Close the bottles to avoid alteration of RT's through evaporation of the mobile phases
Column	The column is installed in the column heater 40°C For the complete UHPLC system the backpressure should not exceed 800 bar. 1 bar = 14.5 PSI

4.3.2 Autosampler Conditions

Injection volume:	25 µL
Sample temperature:	10 °C
Runtime:	4 min
Column temperature:	40 °C ± 2 °C alarm
Needle wash:	post injection wash 12 sec.
Seal Wash:	5 minutes
Wash Solvent:	Autosampler Washing Solution; MeOH

4.3.3 Gradient

Time (min)	**Flow Rate (mL/min)**	**%A**	**%B**	**Curve**
Initial	0.5	50	50	Initial
0.2	0.5	50	50	6
0.25	0.5	0	100	6
0.5	0.5	0	100	6
2	0.5	0	100	6
2.01	0.5	50	50	6
4	0.5	50	50	6

Please note that the gradient is dependent on the analyser used. End users will need to define the optimal gradient for the analyser in use.

4.3.4 MS Conditions (e.g. Waters Xevo TQS)

MS System:	(Waters Xevo TQS)
Ion mode:	Electrospray
Capillary voltage:	2.2 kV
Polarity:	positive
Source temperature:	150 °C
Desolvation temperature:	350°C
Desolvation gas flow:	1000L/hr
Detection mode:	ESI
Dwell time:	0.013 sec
Collision gas:	Argon

Substance	Precursor	Product
Tacrolimus	821.45	768.35
Tacrolimus	821.45	786.4

Substance	Precursor	Product
Tacrolimus C13 D4	826.5	773.5
Tacrolimus C13 D4	826.5	786.4

Substance	Precursor	Product
Sirolimus	931.5	
Sirolimus	931.5	864.4
Sirolimus	931.3	882.35

Substance	Precursor	Product
Sirolimus C13 D3	935.5	864.4
Sirolimus C13 D3	935.5	882.65

Substance	Precursor	Product
Everolimus	975.6	908.45
Everolimus	975.6	926.5
Everolimus	975.6	865.3

Substance	Precursor	Product
Everolimus (C13)2 D4	981.6	914.5
Everolimus (C13)2 D4	981.6	932.6

Substance	Precursor	Product
Cyclosporin A	1202.8	224
Cyclosporin A	1202.8	425.1

Substance	Precursor	Product
Cyclosporin A D12	1214.9	224
Cyclosporin A D12	1214.9	436.3

These conditions are an indication, optimal values can differ slightly between different LC-MS/MS systems.

4.4 Sample Preparation

4.4.1 Reconstitution of the lyophilised Calibrators / Controls.

Refer to paragraph 2.1.1.1 and the product value data sheets.

4.4.2 Sample preparation (whole blood, calibrator or control)

1. Pipette 50 µl sample (Calibrator, Control, Patient sample) into a vial.
2. While mixing on a vortex mixer add 200 µl Zinc Sulphate Solution.
3. Keep mixing and add 500 µl Internal Standard in Deproteinization Solution.
4. Centrifuge (5 min, 10000 x g or more).
5. Pipette the centrifuged supernatant into a vial or 96 well plate, which is suitable for the auto sampler in use and Inject 25 µl in the LC-MS/MS.

4.4.3 Sample Preparation with pipette robot

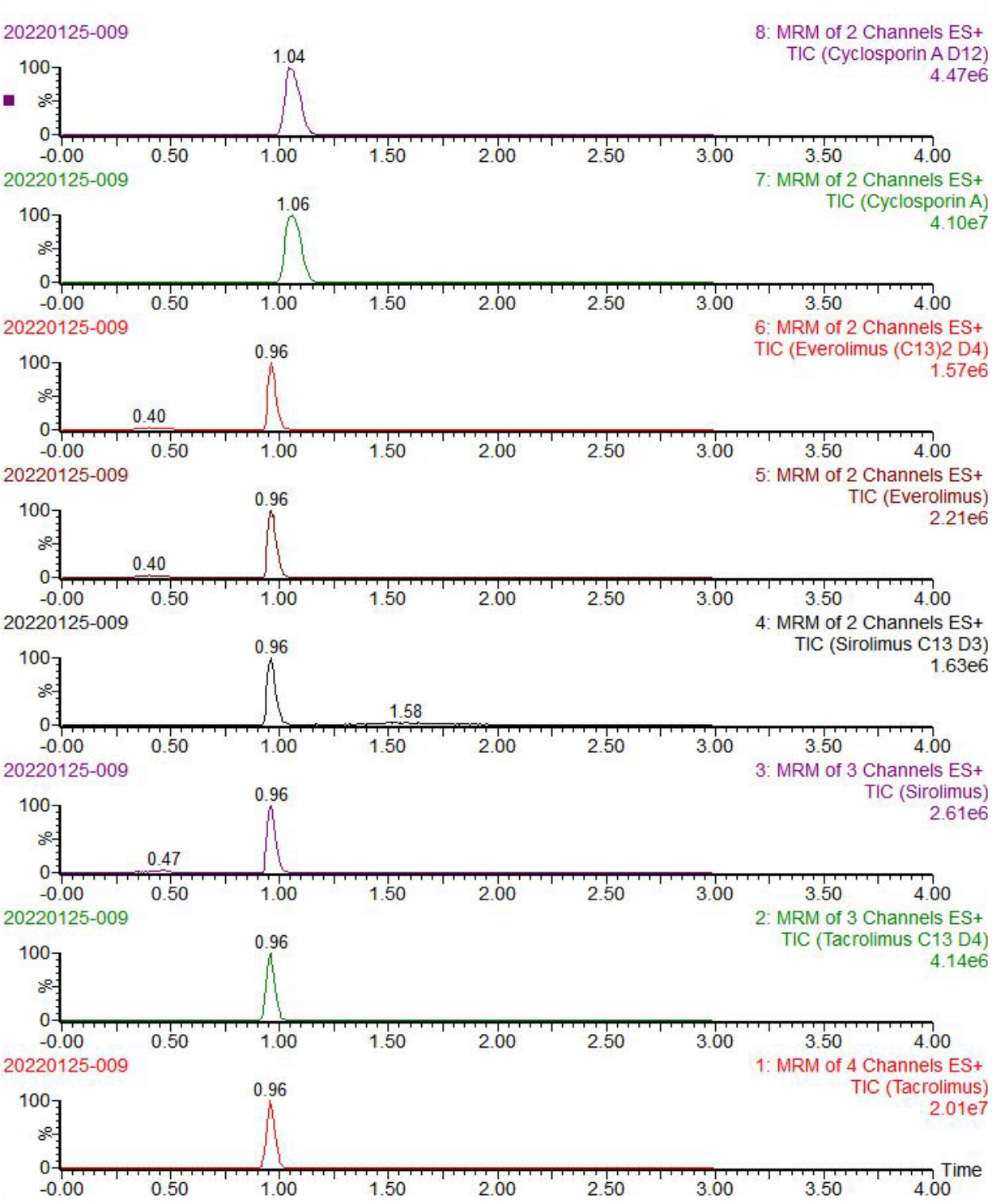
Into a 2 ml 96 well plate:

1. Add 50 µl sample (Calibrator, Control, Patient sample) into a 96 well plate.
2. Whilst mixing the plate, add 200 µl Zinc Sulphate Solution.
3. Whilst continuing to mix the plate, add 500 µl Internal Standard in Deproteinization Solution.
4. Once mixing is complete, centrifuge (5 min , 10000x g or more).
5. Transfer the samples Into a 1 ml 96 well collection plate for injection on the UHPLC/MS/MS system (Needle placement 2 mm) or inject directly off the pellet (Needle placement 10 mm) 25 µl in the LC-MS/MS.

4.5 Interpretation of results

4.5.1 Examples of chromatograms

Example chromatogram of a Patient sample, recorded with a Waters LC-MS/MS TQS:



4.5.2 Results from LC-MS/MS and Reference Values

The assay will result in a certain value for the measurand, which will need to be compared to applicable reference values to be interpreted for the specific patient.

For illustrative purposes only, an example of reference values for this device can be used as follows:

As the measured substances do not naturally occur in the human body scientific literature states the reference values as not applicable. For pharmaceutical substances different levels apply such as regular dosage, upper limit and toxicity. As this information is so (patient) specific and of a technical nature Diagnotix refers to the medical expert under whose authority testing is conducted[1,2,3,4].

The inclusion of this information is required by Annex I, section 20.4.1 (v) of the IVDR. Diagnotix employs no medically trained professionals and can only indicate possible ways of interpreting results based on published scientific literature. Always consult a trained medical professional with expertise in the area of interest for this kit for interpretation of results.

Interpretation of the results of this test also depends in a significant way on the individual characteristics of the patient involved. Diagnotix recommends taking these inputs into consideration as well.

[1] https://tdm-monografie.org/ciclosporine/
[2] https://tdm-monografie.org/everolimus/
[3] https://tdm-monografie.org/sirolimus/
[4] https://tdm-monografie.org/tacrolimus/

5. Summary of Analytical Performance Characteristics

Analytical performance characteristics have been defined by validation of the assay according to IVDR parameters, and using EP Evaluator to extract statistical data from the acquired raw data.

5.1 Repeatability (Simple Precision)

The Repeatability, or Simple Precision, was analyzed by measuring a patient sample, Immunosuppressants control I and Immunosuppressants Calibrator 6 twenty times from one sample within two hours from each other. From these results the Coefficient of Variation (CV) is calculated and compared to the precision verification goal, which in turn calculated and compared to the precision verification goal which is for low samples 10 % and for normal and high samples 7.5 %.

	CV		
Sample	**4193 P IMM Control I Lot: 14H21/07**	**4188 P IMM Calibrator 6 Lot: 14H21/06**	**Patient**
Cylosporin A	2.0 %	2.1 %	1.7 %
Everolimus	5.1 %	1.8 %	3.8 %
Sirolimus	5.5 %	2.2 %	3.2 %
Tacrolimus	3.8 %	1.3 %	1.9 %

5.2 Reproducibility (Complex Precision)

The Reproducibility, or Complex Precision, was analyzed by measuring a patient sample, Immunosuppressants control I and Immunosuppressants Calibrator 6 in duplicate twenty times. Each time the sample preparation had a variance (different analyst, pipet, day, reagent temperature and/or calibration). This to simulate twenty different days in a laboratory. From these results the Coefficient of Variation (CV) is calculated and compared to the precision verification goal which is for low samples 10 % and for normal and high samples 7.5 %.

	CV		
Component	**4193 P IMM Control I Lot: 14H21/07**	**4188 P IMM Calibrator 6 Lot: 14H21/06**	**Patient**
Cylosporin A	4.6 %	4.9 %	5.0 %
Everolimus	6.5 %	5.2 %	7.9 %
Sirolimus	5.3 %	4.3 %	5.5 %
Tacrolimus	3.6 %	5.9 %	4.4 %

5.3 Linearity

The linearity was analyzed by preparing a series of incrementally increasing Immunosuppressants concentrations. These samples were measured in four fold from which the linearity was verified and upper limit of detection was calculated.

Analyte	**Linearity (µg/l)**
Cylosporin A	2500
Everolimus	195
Sirolimus	190
Tacrolimus	200

5.4 Limit of Blank

The Limit of Blank (LOB) was analyzed by measuring Immunosuppressants Calibrator 1 (zero) 20 times and Control I (non-zero) 5 times. From the responses the LOB was calculated.

Analyte	**LOB (µg/l)**
Cylosporin A	0.379
Everolimus	0
Sirolimus	0.817
Tacrolimus	0.0838

5.5 Limit of Quantification

The Limit of Quantification (LOQ) was set to the concentration of the lowest calibrator.

Analyte	**LOQ (µg/l)**
Cylosporin A	< 20
Everolimus	< 1.4
Sirolimus	< 1.5
Tacrolimus	< 1.4

5.6 Carryover

To verify that there is no carryover two samples were prepared. One low (Calibrator 2) and one high (Calibrator 6). The samples were divided into eleven low samples and ten high samples. The samples were measured in a particular order after which the datasets were analyzed.

None of the components showed signs of carryover.

5.7 Accuracy

The accuracy of the method was determined by measuring the equivalent substances from LGC Standards Ltd. This in turn is compared to the results from Diagnotix.

All measured samples met the requirement of +/- 15%.

6. Summary of Clinical Performance Characteristics

Not available at the time of this version of the instructions for use.

7. References

[1] https://tdm-monografie.org/ciclosporine/

[2] https://tdm-monografie.org/everolimus/

[3] https://tdm-monografie.org/sirolimus/

[4] https://tdm-monografie.org/tacrolimus/

[5] Allison. Immunosuppressive Therapy in Transplantation. Nurs Clin North Am. 2016;51(1):107-20

[6] Medication Guidelines for Solid Organ Transplants, BC Transplant Society, Canada 2021

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[10] Summary of product characteristics Rapamunde Available via: https://www.ema.europa.eu

[11] Summary of product characteristics Neoral Available via: https://www.ema.europa.eu

[12] Shipkova et al. Therapeutic Drug Monitoring of Everolimus: A Consensus Report. Therapeutic Drug Monitoring. 2016;38(2):143-69

[13] van Gelder. European Society for Organ Transplantation Advisory Committee recommendations on generic substitution of immunosuppressive drugs. Practice Guideline Transpl Int 2011;24(12):1135-41

[14] Rodríguez-Perálvarez et al. Tacrolimus trough levels, rejection and renal impairment in liver transplantation: a systematic review and meta-analysis. Am J Transplant. 2012;12(10):2797–814

[15] Moes et al. Sirolimus and everolimus in kidney transplantation. Drug Discov Today. 2015;20(10):1243-9

[16] Kahan et al. Therapeutic drug monitoring of sirolimus: correlations with efficacy and toxicity. Clin Transplant 2000;14(2):97-109

[17] Diciolla et al. C2 and C0 values for monitoring cyclosporine therapy in stable heart transplant recipients. Transplantation Proceedings 2005;37:1355-1359

[18] Andrews et al. Cyclosporin: revisions in monitoring guidelines and review of current analytical methods. Ann Clin Biochem. 2002;39:424-35