MATRIKS BIOTEK
innovation for health & wellness

"trace & catch"

Instructions for Use

Infliximab Biosimilar (Remsima®) ELISA

SHIKARI®
Q-REMS

Enzyme immunoassay for the quantitative determination of infliximab biosimilar (Remsima®) in serum and plasma

REF **TR-REMSv1** 12 x8 2-8 ℃

Revision # 1.2 August 2017

CE
IVD

Matriks Biotek® Laboratories
www.matriksbiotek.com

Contents **Page**

	SHIKARI Q-REMS
	Free Infliximab Biosimilar (Remsima®) quantitative analyses
Required Volume (µl)	10
Total Time (min)	70
Sample	Serum, plasma
Sample Number	96
Detection Limit (ng/mL)	100
Spike Recovery (%)	Between 85-115
Shelf Life (year)	1

Intended Use

Enzyme immunoassay for the quantitative determination of **free infliximab biosimilar** (Remsima®) in serum and plasma. *Matriks Biotek® Infliximab ELISA* has been especially developed for the quantitative analysis of free infliximab biosimilar in serum and plasma samples at high specificity.

Summary and Explanation

Remsima™, the world first biosimilar mAb (approved in 2013 by EMA). The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that, in accordance with EU requirements, Remsima has been shown to have a comparable quality, safety and efficacy profile to Remicade. RemsimaTM is a tumor necrosis factor α (TNF-α) antagonist used to treat rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, adult Crohn's disease, plaque psoriasis, and psoriatic arthritis.

Infliximab biosimilar (Remsima®) is a chimeric monoclonal antibody and used to treat auto- immune disorders. Infliximab reduces the amount of active human tumour necrosis factor alpha (hTNFα) in the body by binding to it and preventing it from signaling the receptors for TNFα on the surface of various cell types. TNFα is one of the key cytokines that triggers and sustains the inflammatory reactions. Infliximab is used for the treatment of psoriasis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, and approved by FDA.

Single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Median pharmacokinetic results for doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis and 5 mg/kg in Crohn's disease indicate that the terminal half-life of infliximab is 8.0 to 9.5 days.

In controlled trials, clinical response rates of 20-40% have been achieved with above-mentioned regimens in Crohn's disease and rheumatoid arthritis. However, the therapeutic benefits must be balanced against the risk of a variety of severe adverse events (e.g. severe infections including tuberculosis, hepatotoxicity, infusion reactions,serum sickness-like disease and lymphoma). The volume of distribution of infliximab is low (3-6 L) and represents the intravascular space. Elimination of infliximab is most probably accomplished through degradation by unspecific proteases. It seemed that

methotrexate delayed the decline in the serum concentrations of infliximab. When relating serum concentrations to the clinical response in patients, it can be assumed that through concentrations above 1㎎/mL could be used as a kind of therapeutic target. The rate of clinical remission was higher for patients with a detectable trough serum infliximab compared with patients in whom serum infliximab was undetectable, including those without antibodies. A detectable trough serum infliximab was also associated with a lower C-reactive protein and a higher rate of endoscopic improvement. For Crohn's disease patients treated with scheduled maintenance infusions of infliximab, the serum concentration of infliximab seemed to predict clinical outcome. It was also proposed that, the surveillance of circulating infliximab concentration during maintenance therapy represents an indirect but reliable method to monitor anti-infliximab immunization.

In this context, identification of biomarkers for (non-)response and risk factors for adverse drug reactions relating to serum concentrations and therapeutic drug monitoring of infliximab would be very helpful.

Test Principle

Solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle. Standards and samples (serum or plasma) are incubated in the microtitre plate coated with the reactant for infliximab biosimilar (Remsima®). After incubation, the wells are washed. A horse radish peroxidase (HRP) conjugated probe is added and binds to infliximab captured by the reactant on the surface of the wells. Following incubation wells are washed and the bound enzymatic activity is detected by addition of chromogen-substrate. The colour developed is proportional to the amount of infliximab in the sample or standard. Results of samples can be determined directly using the standard curve.

Warnings and Precautions

1. For professional use only.
2. Before starting the assay, read the instructions completely and carefully. Use the valid version of the package insert provided with the kit. Be sure that everything is understood. For further information (clinical background, test performance, automation protocols, alternative applications, literature, etc.) please refer to the local distributor.
3. In case of severe damage of the kit package please contact Matriks Biotek® or your supplier in written form, latest one week after receiving the kit. Do not use damaged components in test runs, but keep safe for complaint related issues.

п. hōŜè ƒƻű ẏdzƳōŜŊ ŀẏŘ ŜȅLJǻŊè ŘŀűŜ. 5ƻ ẏƻű ƳǻȄ ŊŜŀƎŜẏűă ƻŦ ŘǻŦŦŜŊŜẏű ƒƻűă. 5ƻ ẏƻű dzăŜ ŜȅLJǻŊŜŘ ŊŜŀƎŜẏűă.

p. Cƻƒƒƻǿ ƎƻƻŘ ƒŀōƻŊŀűƻŊè LJŊŀǾűǻǾŜ ŀẏŘ ăŀŦŜűè ƎdzǻŘŜƒǻẏŜă. ² Ŝŀŋ ƒŀō Ǿƻŀűă, ŘǻăLJƻăŀōƒŜ ƒŀűŜȄ Ǝƒƻǿ Ŝă ŀẏŘ LJŊƻűŜǾűǻǿŜ Ǝƒŀăă ǿKŜŋŜ ẏŜǾŜăăŀŊè.

c. wŜŀƎŜẏűă ƻŦ űKǻă ƙǻű Ǿƻẏűŀǻẏǻẏƌ KŀȊŀŊŘdză ƳŀűŜŊǻŀƒ Ƴŀè Ǿŀdză Ŝ ŜèŜ ŀẏŘ ăƙǻẏ ǻŊŊǻűŀűǻƻẏă. {ŜŜ a!¢9wL!{ {¦tt[L95 ŀẏŘ ƒŀōŜƒă Ŧƻŋ ŘŜűŀǻƒă.

т. /KŜƳǻǾŀƒă ŀẏŘ LJŊŜLJŀŊŜŘ ƻŋ dzăŜŘ ŊŜŀƎŜẏűă KŀǿŜ űƻ ōŜ űŋŜŀűŜŘ ŀă KŀȊŀŊŘƻdză ǿŀăűŜ ŀǾǾƻŋŘǻẏƌ űKŜ ẏŀűǻƻẏŀƒ ōǻƻKŀȊŀŊŘ ăŀŦŜűè ƎdzǻŘŜƒǻẏŜă ƻŋ ŊŜƎdzƒŀűǻƻẏă.

у. !ǿƻǻŘ Ǿƻẏűŀǿű ǿǻűK {űƻLJ ăƻƒdzűǻƻẏ. Lű Ƴŀè Ǿŀdză ăƙǻẏ ǻŊŊǻűŀűǻƻẏă ŀẏŘ ōdzŊẏă.

ф. !ƒƒ ŊŜŀƎŜẏűă ƻŦ űKǻă ƙǻű Ǿƻẏűŀǻẏǻẏƌ KdzƳŀẏ ăŜŊdzƳ ƻŋ LJƒŀăƳŀ ό!Ŝ. ăűŀẏŘŀŋŘăύ KŀǿŜ ōŜŜẏ űŜăűŜŘ ŀẏŘ ǿŜŋŜ Ŧƻdzẏ ẏŜƎŀűǿŜ Ŧƻŋ I.±ǊL, I.ă!Ǝ ŀẏŘ I/±. Iƻǿ ŜǿŜŋ, ŀ LJŊŜăŜẏǾŜ ƻŦ űKŜăŜ ƻŋ ƻűKŜŋ ǻẏŦŜǾűǻƻdză ŀƎŜẏűă Ǿŀẏƻű ōŜ ŜȄǾƒdzŘŜŘ ŀōăƻƒdzűŜƒè ŀẏŘ űKŜŋŜŦƻŋŜ ŊŜŀƎŜẏűă ăKƻdzƒŘ ōŜ űŋŜŀűŜŘ ŀă LJƻűŜẏűǻŀƒ ōǻƻKŀȊŀŊŘă ǻẏ dzăŜ ŀẏŘ Ŧƻŋ ŘǻăLJƻăŀƒ.

мл. {ƻƳŜ ŊŜŀƎŜẏűă Ǿƻẏűŀǻẏ ăƻŘǻdzƳ ŀȊǻŘŜ όbŀb$_3$ύ ŀă LJŊŜăŜŋǿŀűǻǿŜă. Lẏ Ǿŀă Ŝ ƻŦ Ǿƻẏűŀǿű ǿǻűK ŜèŜă ƻŋ ăƙǻẏ, Ŧƒdză K ǻƳƳŜŘǻŀűŜƒè ǿǻűK ǿŀűŜŋ. bŀb$_3$ Ƴŀè ŊŜŀǾű ǿǻűK ƒŜŀŘ ŀẏŘ ǾƻLJLJŜŋ LJƒdzƳōǻẏƌ űƻ Ŧƻŋƙ ŜȄLJƒƻăǻǿŜ ƳŜűŀƒ ŀȊǻŘŜă. ² KŜẏ ŘǻăLJƻăǻẏƌ ŊŜŀƎŜẏűă, Ŧƒdză K ǿǻűK ƒŀŋƎŜ ǿƻƒdzƳŜ ƻŦ ǿŀűŜŋ űƻ ŀǿƻǻŘ ŀȊǻŘŜ ōdzǻƒŘdzLJ.

Storage and Stability

¢KŜ ƙǻű ǻă ăKǻLJLJŜŘ ŀű ŀƳōǻŜẏű űŜƳLJŜŊŀűdzŊŜ ŀẏŘ ăKƻdzƒŘ ōŜ ăűƻŊŜŘ ŀű нпус/. YŜŜLJ ŀǿŀè Ŧŋƻƴ KŜŀű ƻŋ ŘǻŊŜǾű ădzẏƒǻƎKű. ¢KŜ ăűƻŊŀƎŜ ƻŦ ƳǻǾŋƻűǻűŜŊ LJƒŀűŜ ǻă ăűŀōƒŜ dzLJ űƻ űKŜ ŜȄLJǻŊè ŘŀűŜ ƻŦ űKŜ ƙǻű ǻẏ űKŜ ōŊƻǿŜ, ōdzű ǻƎKűƒè Ǿƒƻă ŜŘ ōŀƎ ǿKŜẏ ăűƻŊŜŘ ŀű нςус/.

Specimen Collection and Storage

Serum, Plasma (EDTA, Heparin*)

¢KŜ dzădzŀƒ LJŊŜǾŀdzűǻƻẏă Ŧƻŋ ǿŜẏǻLJdzẏǾűdzŊŜ ăKƻdzƒŘ ōŜ ƻōăŜŊǿŜŘ. Lű ǻă ǻƳLJƻŊűŀẏű űƻ LJŊŜăŜŊǿŜ űKŜ ǾKŜƳǻǾŀƒ ǻẏűŜƎŊǻűè ƻŦ ŀ ōƒƻƻŘ ăLJŜǾǻƳŜẏ Ŧŋƻƴ űKŜ ƳƻƳŜẏű ǻű ǻă Ǿƻƒƒ ŜǾűŜŘ dzẏűǻƒ ǻű ǻă ŀăăŀèŜŘ. 5ƻ ẏƻű dzăŜ ƎŊƻăăƒè KŜƳƻƒèǻǾ, ǻǾűŜŊǻǾ ƻŋ ƎŊƻăăƒè ƒǻLJŜƳǻǾ ăLJŜǾǻƳŜẏă. {ŀƳLJƒŜă ŀLJLJŜŀŊǻẏƌ űdzŊōǻŘ ăKƻdzƒŘ ōŜ ǾŜẏűŊǻŦdzƎŜŘ ōŜŦƻŊŜ űŜăűǻẏƌ űƻ ŊŜƳƻǿŜ ŀẏè LJŀŊűǻǾdzƒŀűŜ ƳŀűŜŊǻŀƒ.

*Infliximab biosimilar (Remsima®) infusion camouflages/masks the presence of antibody to infliximab biosimilar in serum/plasma samples. Therefore, blood sampling time is critical for detection of infliximab biosimilar. Matriks Biotek® Laboratories propose to obtain blood sample just before the infusion of infliximab biosimilar (Remsima®) or at least 2 weeks after the infusion of infliximab biosimilar (Remsima®).

Storage:	2-8°C	-20°C	Keep away from heat or direct sun light Avoid repeated freeze-thaw cycles
Stability:	2 d	6 mon	

Materials Supplied

1 x 12 x 8	MTP	**Microtiter Plate** Break apart strips. Microtiter plate with 12 rows each of 8 wells coated with reactant.
7 x 0.3 mL	STND A-E HIGH CNTRL LOW CNTRL	**Infliximab Standards A-E, High Level Control, Low Level Control** 3; 1; 0.3; 0.1; 0 microgram/mL Ready to use. Used for construction of the standard curve. Contains infliximab biosimilar (Remsima®), human serum, stabilizer and <0.1% NaN_3.
1 x 50 mL	ASSAY BUF	**Assay Buffer** Blue colored. Ready to use. Contains proteins and <0.1% NaN_3.
1 x 12 mL	HRP CONJ	**Horse radish peroxidase-Conjugated Probe** Red colored. Ready to use. Contains HRP-probe, stabilizer and <0.1% NaN_3.
1 x 12 mL	TMB SUBS	**TMB Substrate Solution** Ready to use. Contains TMB
1 x 12 mL	TMB STOP	**TMB Stop Solution** Ready to use. 1N HCl.
1 x 50 mL	WASHBUF CONC	**Wash Buffer**, Concentrate (20x) Contains Buffer with Tween 20.
2 x 1	FOIL	**Adhesive Foil** For covering of Microtiter Plate during incubation.
2 x 1	SLGP	**Semi-Log Graph Paper** For constructing standard curve and calculation of results.

Materials Required but not Supplied

1. Micropipettes (Multipette Eppendorf or similar devices, < 3% CV).
2. Calibrated measures.
3. Tubes (1 mL) for sample dilution.
4. Wash bottle, automated or semi-automated microtiter plate washing system
5. Microtiter plate reader capable of reading absorbance at 450/650 nm.
6. Bidistilled or deionised water, paper towels, pipette tips and timer.

Procedure Notes

1. Any improper handling of samples or modification of the test procedure may influence the results. The indicated pipetting volumes, incubation times, temperatures and pretreatment steps have to be performed strictly according to the instructions. Use calibrated pipettes and devices only.
2. Once the test has been started, all steps should be completed without interruption. Make sure that required reagents, materials and devices are prepared ready at the appropriate time. Allow all reagents and specimens to reach room temperature (18-25 °C) and gently swirl each vial of liquid reagent and sample before use. Mix reagents without foaming.
3. Avoid contamination of reagents, pipettes and wells/tubes. Use new disposable plastic pipette tips for each reagent, standard or specimen. Do not interchange caps. Always cap not used vials. Do not reuse wells/tubes or reagents.
4. Use a pipetting scheme to verify an appropriate plate layout.
5. Incubation time affects results. All wells should be handled in the same order and time sequences. It is recommended to use an 8-channel Micropipettor for pipetting of solutions in all wells.
6. Microplate washing is important. Improperly washed wells will give erroneous results. It is recommended to use a multichannel pipette or an automatic microplate washing system. Do not allow the wells to dry between incubations. Do not scratch coated wells during rinsing and aspiration. Rinse and fill all reagents with care. While rinsing, check that all wells are filled precisely with Wash Buffer, and that there are no residues in the wells.

7. Humidity affects the coated wells/tubes. Do not open the pouch until it reaches room temperature. Unused wells/tubes should be returned immediately to the resealed pouch including the desiccant.

Pre-Test Setup Instructions

1. Preparation of Components

Dilute/ disolve	Component	with	Diluent	Relation	Remarks	Storage	Stability
10 mL	Wash Buffer*	Up to 200 mL	bidist. Water	1:20	Warm up at 37°C to dissolve crystals. Mix vigorously.	2-8 °C	2 w

***.** Prepare Wash Buffer before starting assay procedure.

2. Dilution of Samples

Sample	To be diluted	With	Relation	Remarks
Serum/ Plasma	Initially 1:20	Assay Buffer	1:20-1:100	For dilution at 1:20; 10µL Sample + 190µL Assay Buffer For dilution at 1:100; 5µL Sample + 495µL Assay Buffer

Patient samples with a concentration of infliximab above the measuring range are to be rated as > "Highest Standard (Standard A)". The result must not be extrapolated. The patient sample in question should be further diluted with Assay Buffer and retested.

Test Procedure

1	Pipette 100µl of Assay Buffer non-exceptionally into each of the wells to be used.
2	Pipette 10 µL of each **ready-to use Standards, High Level Control, Low Level Control and Diluted Samples** into the respective wells of microtiter plate. **Wells** A1: Standard A B1: Standard B C1: Standard C D1: Standard D E1: Standard E F1: High Level Control G1: Low Level Control H1 and on: Sample (Serum / Plasma)
3	Cover the plate with adhesive foil. Incubate 30 min at room temperature (18-25°C).
4	Remove adhesive foil. Discard incubation solution. Wash plate 3 times each with 300 µL of diluted Wash Buffer. Remove excess solution by tapping the inverted plate on a paper towel.
5	Pipette 100 µL of ready-to use HRP-Conjugated Probe into each well.
6	Cover the plate with adhesive foil. Incubate 30 min at room temperature (18-25°C).
7	Remove adhesive foil. Discard incubation solution. Wash plate 3 times each with 300 µL of diluted Wash Buffer. Remove excess solution by tapping the inverted plate on a paper towel.
8	Pipette 100 µL of TMB Substrate Solution into each well.
9	Incubate 10 min (without adhesive foil.) at room temperature (18-25°C) in the dark.
10	Stop the substrate reaction by adding 100 µL of Stop Solution into each well. Briefly mix contents by gently shaking the plate. Color changes from blue to yellow.
11	Measure optical density with a photometer at 450/650 nm within 30 min after pipetting of the Stop Solution.

Quality Control

The test results are only valid only if the test has been performed following the instructions. Moreover the user must strictly adhere to the rules of GLP (Good Laboratory Practice) or other applicable standards/laws. All standards must be found within the acceptable ranges as stated above and/or label. If the criteria are not met, the run is not valid and should be repeated. In case of any deviation the following technical issues should be proven: Expiration dates of (prepared) reagents, storage conditions, pipettes, devices, incubation conditions and washing methods.

Calculation & Interpretation of Results

1. Using the standards (3; 1; 0.3; 0.1; 0 µg/mL) disregarding zero standard, construct a standard curve by plotting the OD450/650 nm for each of 4 standards on the vertical (Y-axis) axis versus the corresponding infliximab biosimilar concentration on the horizontal (X-axis) axis, thus creating a standard curve by 4 points obtained.

2. The concentration of the samples can be read directly from this standard curve. Using the absorbance value for each sample, determine the corresponding concentration of infliximab from the standard curve. Find the absorbance value on the Y-axis and extend a horizontal line to the curve. At the point of intersection, extend a vertical line to the X-axis and read the infliximab biosimilar concentration for the unknown sample.

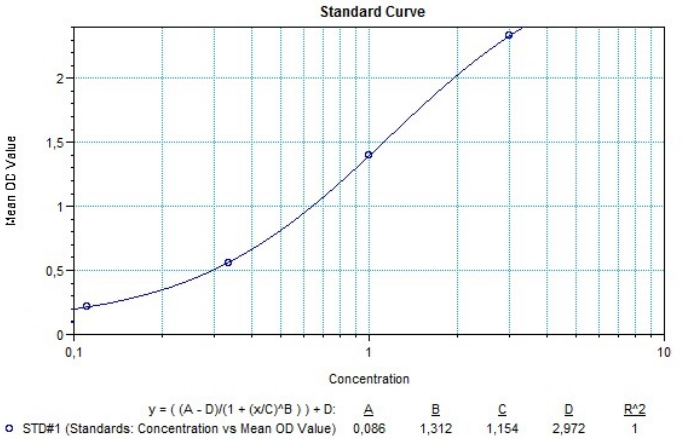
3. If computer data regation is going to be used, we recommend primarily "4 Parameter Logistic (4PL)" or secondly the "point-to-point calculation".

4. To obtain the exact values of the samples, the concentration determined from the standard-curve must be multiplied by the dilution factor (20x). Any sample reading greater than the highest standard should be further diluted appropriately with Assay Buffer and retested. Therefore, if the pre-diluted samples have been further diluted, the concentration determind from the standard curve must be multiplied by the further dilution factor.

   E.g.; *If the pre-diluted sample further diluted in a ratio of 1:5 then results should be multiplied by 100.*

5. Automated method: Computer programs can also generally give a good fit.

Typical Calibration Curve
(Example. Do not use for calculation!)



Standard	Concentration (ug/mL)	Mean OD450/650
A	3	2,332
B	1	1,395
C	0,3	0,560
D	0.1	0,214
E	0	0,032

Assay Characteristics

1. **Specificity:** Except for the other therapeutic anti-TNF antibodies such as etanercept (Enbrel®) and/or adalimumab (Humira®) with which cross reaction might occur to some extends, there is no cross reaction with native serum immunoglobulin.

2. **Sensitivity:** The lowest detectable level that can be distinguished from the zero standard is 5 ng/mL.

3. **Precision Of Kit:**
   Intra-assay CV: <15% for infliximab biosimilar range 0.1-3 µg/mL.
   Inter-assay CV: <15% for infliximab biosimilar range 0.1-3 µg/mL.

4. Recovery: Recovery rate was found to be between 85-115% with normal human serum samples with known concentrations.

Automation

Experiments have shown that the *Matriks Biotek®* SHIKARI® Infliximab Biosimilar (Remsima®) ELISA is also suitable to run on an automated ELISA processor.

References

1. Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Bijl H, Woody JN, Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2) in patients with rheumatoid arthritis, Lancet, 1994; Oct 22;344(8930):1125-7.

2. Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, Leeb B, Breedveld FC, Macfarlane JD, Bijl H, et al., Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet, Oct 22;344(8930):1105-10.

3. Keating GM, Perry CM, infliximab: an updated review of its use in Crohn's disease and rheumatoid arthritis, BioDrugs, 2002;16(2):111-48.

4. Lyseng-Williamson KA, Foster RH, infliximab: a pharmacoeconomic review of its use in rheumatoid arthritis, Pharmacoeconomics, 2004;22(2):107-32.

5. Maini RN, Elliott MJ, Brennan FM, Williams RO, Chu CQ, Paleolog E, Charles PJ, Taylor PC, Feldmann M, Monoclonal anti-TNF alpha antibody as a probe of pathogenesis and therapy of rheumatoid disease, Immunol Rev, 1995 Apr;144:195-223.

6. Xu Z, Seitz K, Fasanmade A, Ford J, Williamson P, Xu W, Davis HM, Zhou H, Population pharmacokinetics of infliximab in patients with ankylosing spondylitis, J Clin Pharmacol, 2008 Jun;48(6):681-95. Epub 2008 Apr 9.

7. Caviglia R, Boskoski I, Cicala M, Long-term treatment with infliximab in inflammatory bowel disease: safety and tolerability issues, Expert Opin Drug Saf, 2008 Sep;7(5):617-32.

8. Reddy JG, Loftus EV Jr, Safety of infliximab and other biologic agents in the inflammatory bowel diseases, Gastroenterol Clin North Am, 2006 Dec;35(4):837-55.

9. Klotz U, Teml A, Schwab M, Clinical pharmacokinetics and use of infliximab, Clin Pharmacokinet, 2007; 46(8): 645-660.

10. Maser EA, Villela R, Silverberg MS, Greenberg GR, Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease, Clin Gastroenterol Hepatol, 2006 Oct;4(10):1248-1254.

11. Reimold AM, New indications for treatment of chronic inflammation by TNF-alpha blockade, Am J Med Sci, 2003 Feb;325(2):75-92.

12. Ternant D, Mulleman D, Degenne D, Willot S, Guillaumin JM, Watier H, Goupille P, Paintaud G, An enzyme-linked immunosorbent assay for therapeutic drug monitoring of infliximab, Ther Drug Monit, 2006 Apr;28(2):169-174.

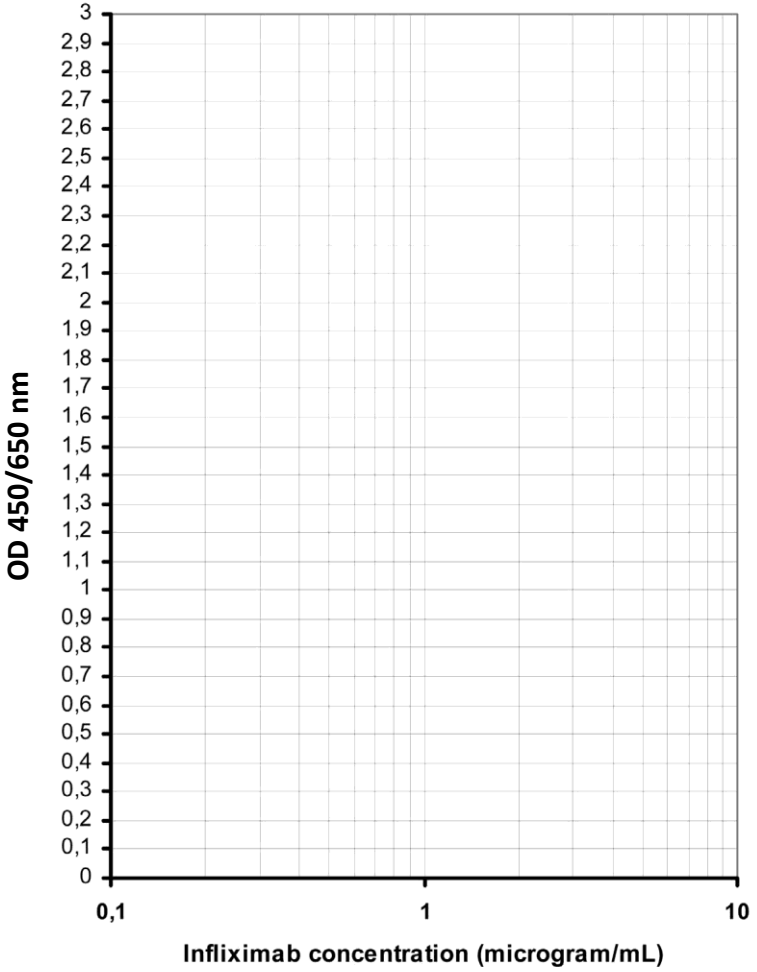
13. Candon S, Mosca A, Ruemmele F, Goulet O, Chatenoud L, Jean-Pierre Ce´zard, Clinical and biological consequences of immunization to infliximab in pediatric Crohn's disease, Clinical Immunology, 2006; 118: 11-19.

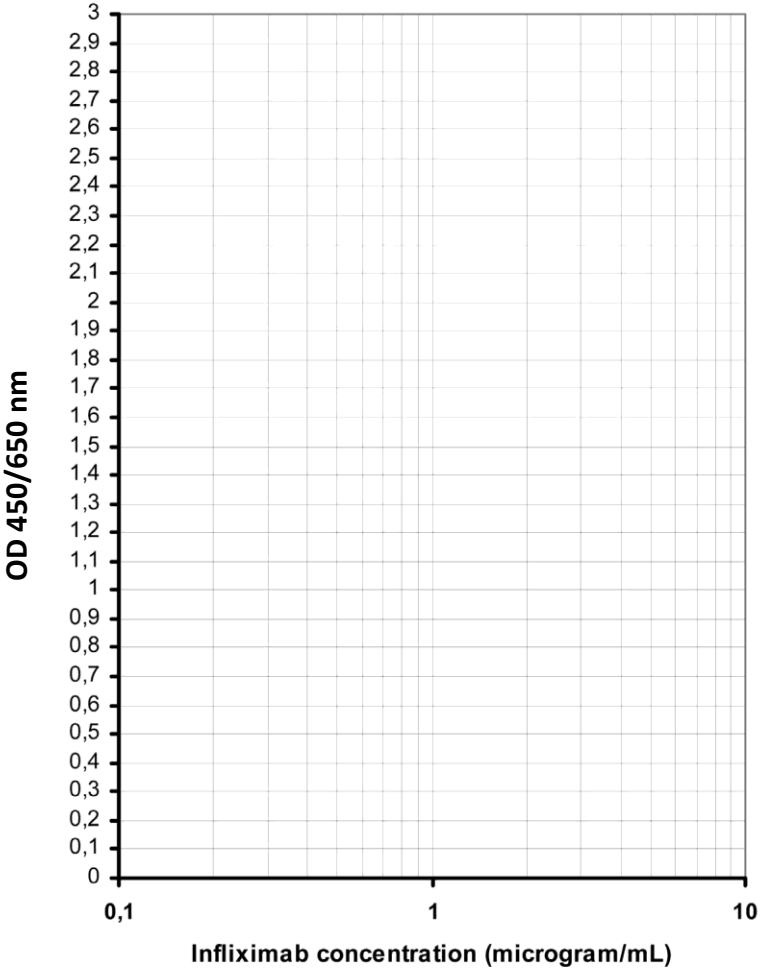
14. Gottlieb AB, Masud S, Ramamurthi R, Abdulghani A, Romano P. Et al., Pharmacodynamic and pharmacokinetic response to anti-tumor necrosis factor-monoclonal antibody (infliximab) treatment of moderate to severe psoriasis vulgaris, J Am Acad Dermatol 2003;48: 68-75.

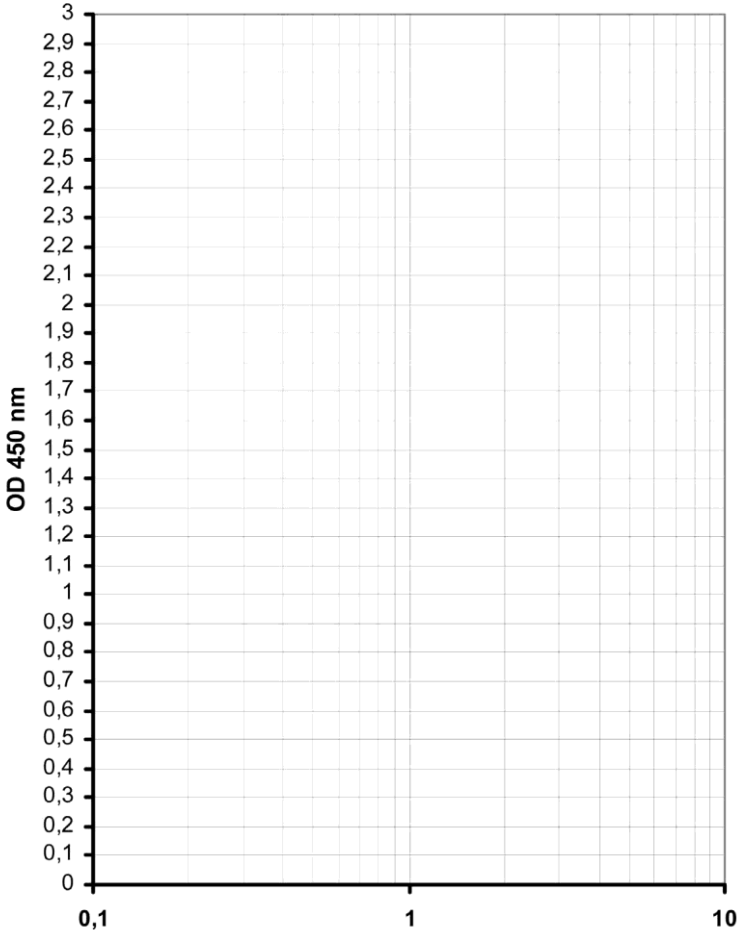
15. Maini RN, Breedveld FC, Kalden JR, Smolen JS, et al., Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor a monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis,

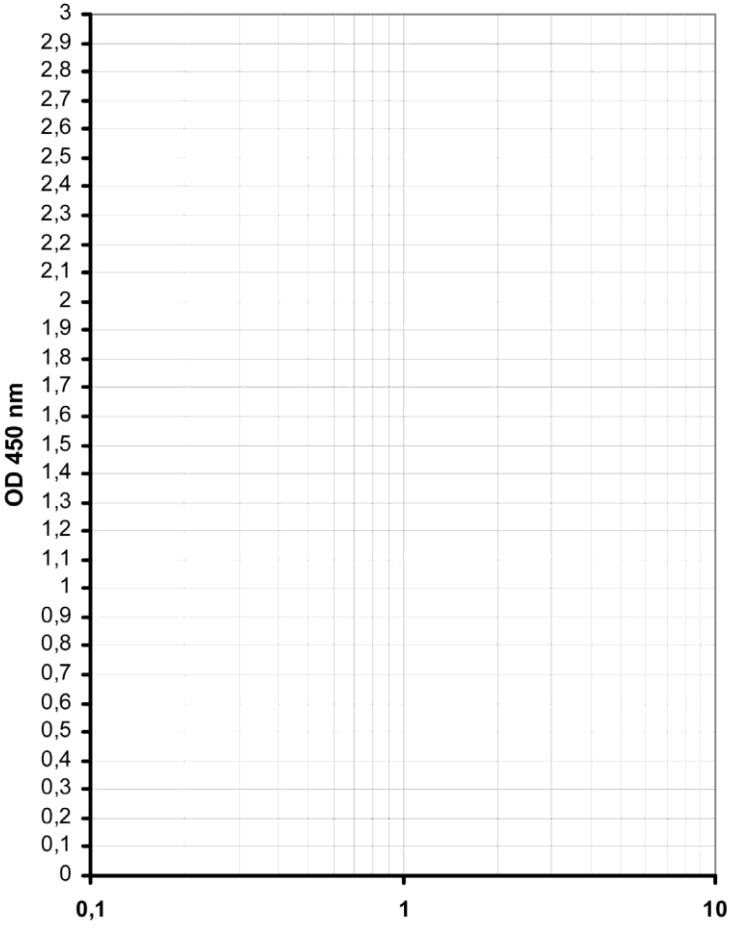
Arthritis & Rheumatism, 1998; 41: 1552-1563.

16. Xu Z, Seitz K, Fasanmade A, Ford J, Williamson P, Xu W, Davis HM, et al. Population Pharmacokinetics of infliximab in Patients With Ankylosing Spondylitis, J. Clin. Pharmacol. 2008; 48; 681-695.


OD 450/650 nm
3
2,9
2,8
2,7
2,6
2,5
2,4
2,3
2,2
2,1
2
1,9
1,8
1,7
1,6
1,5
1,4
1,3
1,2
1,1
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,1
1
10
Infliximab concentration (microgram/mL)


OD 450/650 nm
3
2,9
2,8
2,7
2,6
2,5
2,4
2,3
2,2
2,1
2
1,9
1,8
1,7
1,6
1,5
1,4
1,3
1,2
1,1
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,1
1
10
Infliximab concentration (microgram/mL)


OD 450 nm
3
2,9
2,8
2,7
2,6
2,5
2,4
2,3
2,2
2,1
2
1,9
1,8
1,7
1,6
1,5
1,4
1,3
1,2
1,1
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,1
1
10


OD 450 nm
3
2,9
2,8
2,7
2,6
2,5
2,4
2,3
2,2
2,1
2
1,9
1,8
1,7
1,6
1,5
1,4
1,3
1,2
1,1
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,1
1
10