EliA™

ANA Differentiation

Sm, U1RNP, RNP70, Ro, La, Scl-70, CENP, Jo-1

EliA™

Excellence in Autoimmunity

EliA™ ANA Differentiation – A Clearer Picture in Connective Tissue Diseases

High clinical relevance

- high sensitivity supports diagnosis
- high specificity reduces inappropriate follow-up

High technical performance

- low variances and high reproducibility for consistent results
- high lot-to-lot consistency due to validated production procedures
- minimal lot changes from large production lots
- high capacity antigen production ensures long-term, stable supply
- semi-quantitative results expressed as a ratio relative to a defined calibrator

State-of-the-art antigens

- highly purified SmD protein
- human recombinant U1RNP (mixture of recombinant RNP70, A, C)
- human recombinant RNP70
- human recombinant Ro (52, 60kDa)
- human recombinant La
- human recombinant Scl-70
- human recombinant CENP-B
- human recombinant Jo-1

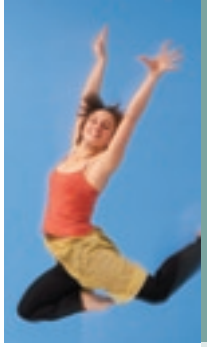
Automation

- screen and individual specificity testing available in one run
- choice of ImmunoCAP™ instruments available for low to high throughput
- stored standard curve to be used with all EliA™ IgG analytes
- urgent samples can be run cost-efficiently
- reflex testing from screen to single-specificity assays

Easy Handling

- serum as well as plasma can be used
- automated sample dilution

The EliA™ System



Time for the Essentials

- completely automated (true walk-away, overnight runs)
- easy instrument management by ImmunoCAP™ Data Manager (IDM) software
- barcode-reader
- protocols, QC and raw data easily accessible
- optional host link
- detailed QC management
- integrated stock management system on the ImmunoCAP™ 250

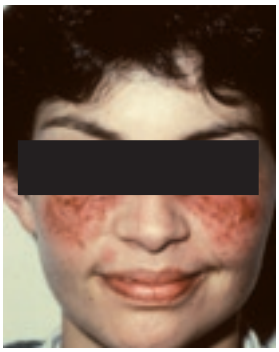
Cost efficient and flexible

- autoimmunity and allergy on the same instrument, in the same run
- different autoimmune tests in the same run
- no batching of samples necessary – small runs can be handled cost-effectively
- once-monthly calibration – curve control each run
- from one to five ImmunoCAP™ instruments may be linked into one IDM computer

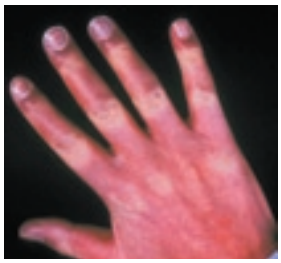
A boost in service for your laboratory and your clinicians

- sample – result turnaround the same day
- STAT function on ImmunoCAP™ 250 for immediate testing of emergency samples
- overnight runs possible
- detailed documentation of results (patient or requester specific)
- ImmunoCAP™ 100 – up to 46 determinations in less than 2.5 hours
- ImmunoCAP™ 250 – fully automated random access – up to 350 determinations per shift
- multiple methods in one run
- positive identification and traceability of samples and reagents on ImmunoCAP™ 250

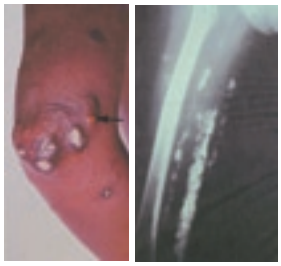
Connective Tissue Diseases



Picture 1: *SLE, butterfly rash*



Picture 2: *Raynaud's phenomenon*



Picture 3: *Dermatomyositis, calcification*

Connective Tissue diseases (CTDs) represent classical models of systemic autoimmune diseases. They are a heterogeneous group of diseases characterised by abnormal structure or function of one or more of the elements of connective tissue, i.e. collagen, elastin or the mucopolysaccharides. Differential diagnosis of CTDs is mainly based on clinical findings but is complicated by the similarity of their symptoms. Therefore, autoantibodies are useful markers to support the diagnosis or exclusion of CTDs. The most prominent CTDs are systemic lupus erythematosus (SLE; potentially affecting all organs), Sjögren's syndrome (SS; characterised by diminished lacrimal and salivary gland secretions), scleroderma (systemic sclerosis, SSc; a chronic, progressive dermatosis), limited systemic sclerosis (a scleroderma formerly known as CREST syndrome, with a more benign disease course), poly-/dermatomyositis (PM/DM; an acute or chronic inflammatory disease of muscle and skin), and mixed connective tissue disease (MCTD; a syndrome with features of scleroderma, rheumatoid arthritis, SLE and PM/DM).

Disease Markers

The presence and specificity of certain autoantibodies give a strong indication as to the likely CTD involved. The prevalence of marker autoantibodies in particular CTDs are summarised in Table 1.

Marker Autoantibody	Associated CTD	Autoantibody Prevalence
Sm	SLE	20–30%
U1RNP	MCTD, SLE	100%, 30–40%
RNP70	MCTD, SLE	75–95%, 10–15%
SS-A/Ro	Sjögren's syndrome, SLE	60–90%, 40–50%
SS-B/La	Sjögren's syndrome, SLE	50–95%, 6–15%
Scl-70	Systemic sclerosis	30–60%
CENP	Limited systemic sclerosis (CREST), Primary biliary cirrhosis (PBC)	70–80% 10–20%
Jo-1	Poly-/dermatomyositis	25–35%

Table 1: *Prevalence of autoantibodies in connective tissue diseases.*

EliA™ ANA Panel Antigens

Phadia autoimmune assays are developed "clinically" in order to maximise the assays' usefulness in a diagnostic setting. All antigens are selected on the basis of the related antibody's significance in one or more of the connective tissue diseases. The result is clinically relevant, sensitive and highly specific differentiation assays.

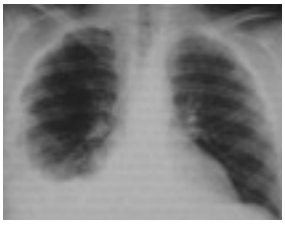
- **Recombinant antigens from the eukaryotic Baculovirus/insect cell system for best quality, consistency and performance**

As an intact three-dimensional structure of the antigens (conformation) is crucial for recognition by antibodies, our human recombinant antigens are produced in the eukaryotic baculovirus/insect cells system which, in contrast to bacterial systems, is capable of expressing the antigens in the correct conformation and performing the complex post-translational modifications necessary to ensure the protein is antigenically identical to the human native form. Using recombinant antigens wherever possible allows us to minimise contaminants, avoid harsh, protein-altering purification processes and guarantee a high lot-to-lot consistency of the antigens.

The EliA system measures specific antibodies against a calibration system of WHO immunoglobulin standards. Lot-specific conversion factors convert the measured response units (RU) to µg/l and thence to the EliA unit result and ensure consistency between runs and over different lots.

Sm, U1RNP, RNP70

Sm antibodies offer a highly specific but comparatively insensitive clinical marker for SLE.
Indeed, their presence constitutes one of the revised ACR criteria for its diagnosis even though their overall prevalence in SLE patients ranges between only 20 and 30%.
U1snRNP antibodies typically occur in both SLE and MCTD. However, in MCTD the presence of U1snRNP antibodies is required for diagnosis whereas in SLE they occur in only 30-40% of patients. Although the anti-U1snRNP immune response targets all three protein components (70kDa, A, C), 70kDa antibodies, particularly when present in high titers may be more specific for MCTD as they have been reported to be less frequent in SLE (approx. 12%) than those to the proteins A or C (approx. 23%). However, there are also cases of MCTD with only antibodies to proteins A and/or C and without any 70kDa antibodies.



Picture 4: *SLE, pleural effusions in lung x-ray*

Targeted antigen selection for maximum clinical relevance

EliA™Sm, EliA™U1RNP and EliA™RNP70 Antigens

The uracil-rich small nuclear ribonucleoproteins (UsnRNP) U1,U2,U4,U5 and U6 all contain a group of proteins, the so-called Sm peptides with the major antigenic targets being the B and D proteins. In contrast, the proteins 70kDa, A and C only occur in the U1snRNP. Because of cross-reactivity between antibodies to the U1-specific A and C and those directed to the SmB/B' proteins, up to 60% of anti-U1snRNP sera may also react with B/B'. As a consequence, only the presence of anti-SmD and/or the presence of anti-Sm in the absence of anti-A and anti-C can be regarded as characteristic for an anti-Sm sample.
EliA Sm uses highly purified SmD as the coating antigen and thus assures a high clinical specificity for SLE.

High specificity

For the detection of antibodies to U1snRNP, the EliA system offers the choice between EliA U1RNP, containing a mixture of the human recombinant proteins 70kDa, A and C or EliA RNP70 which only uses the 70kDa protein. This means that you can screen for all U1snRNP antibodies (EliA U1RNP) or choose to detect the more MCTD specific ones (EliA RNP70).

Choice of screen test or MCTD-specific assay

Normal Range and Measuring Range

Studies to determine the normal range utilised serum from a large number of subjects. For EliA Sm, EliA U1RNP and EliA RNP70, the following values were obtained.

	EliA Sm	EliA U1RNP	EliA RNP70
Normal Range			
Negative	<5 EliA U/ml	<5 EliA U/ml	<7 EliA U/ml
Equivocal	5–10 EliA U/ml	5–10 EliA U/ml	7–10 EliA U/ml
Positive	>10 EliA U/ml	>10 EliA U/ml	>10 EliA U/ml
Measuring Range	0.1– ≥120 EliA U/ml	0.3– ≥240 EliA U/ml	0.3– ≥240 EliA U/ml

To guarantee a high consistency in results, the EliA system uses lot-specific conversion factors to calculate EliA U/ml from the original fluorescence response units. Therefore the upper limit of the measuring range for EliA assays may vary from lot to lot.

Ro (SS-A), La (SS-B)

Antibodies to Ro 52 and Ro60 are both important

The detection of Ro (SS-A) antibodies is of interest and clinical significance for the diagnosis of Sjögren's syndrome (prevalence 60-75% for primary SS, about 80% for secondary SS) and SLE (prevalence 40-50%). They have been reported to occur in tight association with certain disease subsets such as subacute cutaneous LE, neonatal LE or vasculitis in Sjögren's syndrome. As anti-Ro (SS-A) may be the only antibody present in many patients with SLE or SS, failure to detect these antibodies leaves a diagnostic void. The complete Ro antigen comprises two proteins, Ro52 and Ro60. Most of the Ro positive patients show antibodies to both Ro60 and Ro52. However, as was shown in the studies summarised below, there are subsets of patients who only produce antibodies to Ro52 or to Ro60. Newborn children of female patients with Ro52 antibodies are known to have a high risk for congenital heart block. Thus a diagnostic test for Ro antibodies should include both antigens, Ro60 and Ro52.

La (SS-B) antibodies are the serological hallmark of Sjögren's syndrome although a small proportion of patients remains anti-La negative. Reported in 6 – 16% of sera from SLE patients, La antibodies are associated with a lower prevalence for both dsDNA antibodies and renal disease. Although a strong association of neonatal LE with anti-Ro was recognized first, the majority of mothers of babies with neonatal SLE are known to also have anti-La.

	Preliminary European classification criteria of 1993 (Vitali et al.,1993) **n=100**	Revised European classification criteria of 2002 (Vitali et al.,2002) **n=66**
Serum autoantibodies	**No. of Sjögren's syndrome patients in %**	**No. of Sjögren's syndrome patients in %**
Ro52 alone	20	15
Total with Ro 52	62	71
Ro60 alone	0	0
Total with Ro60	24	33
La48 alone	4	3
Total with La48	45	56
Ro52+La48	20	24
Ro60+La48	2	2
Ro52+Ro60	3	5
Ro52+Ro60+La48	19	27

Table 2: *Prevalence of Ro52,Ro60 and La48 antibodies in Sjögren's syndrome patients. European classification criteria of 1993 and 2002 (Taken from Garberg et al., 2005).*

EliA™ Ro and EliA™ La Antigens

Ro60 and Ro52 included for maximum sensitivity – especially for neonatal lupus

EliA Ro uses a mixture of human recombinant SS-A/Ro60 and SS-A/Ro52 proteins. On the EliA La solid phase, human recombinant SS-B/La protein is coated. These recombinant proteins are produced in the Baculovirus/insect cell system.

Normal Range and Measuring Range

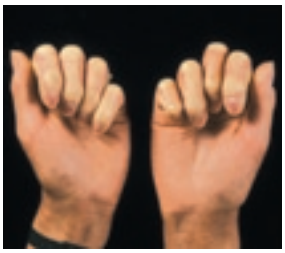
Studies to determine the normal range utilised serum from a large number of subjects. For EliA Ro and EliA La, the following values were obtained.

	EliA Ro	EliA La
Normal Range		
Negative	<7 EliA U/ml	<7 EliA U/ml
Equivocal	7–10 EliA U/ml	7–10 EliA U/ml
Positive	>10 EliA U/ml	>10 EliA U/ml
Measuring Range	0.3– ≥240 EliA U/ml	0.3– ≥320 EliA U/ml

Scl-70, CENP

Systemic Sclerosis (Scleroderma, SSc) is a generalized connective tissue disease which affects the skin and some internal organs. The presentation and severity of the disease varies significantly from patient to patient and is generally classified as either diffuse or limited. Antibodies to Scl-70 are characteristic and specific for SSc. Between 20-60% of patients with diffuse scleroderma have this antibody and its presence is associated with lung involvement. The antibody is almost never seen in normal individuals or in individuals with other connective tissue diseases and the level correlates with disease activity and severity so it has significant clinical importance in the diagnosis and prognosis of SSc.

CENP (Centromere Protein) antibodies are found in 70-90% of patients with a limited form of scleroderma previously termed CREST (Calicinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasis) syndrome, with a comparatively favourable prognosis. They are rarely seen in diffuse Systemic Scleroderma so their detection is important. However, they may also occur in primary Raynaud's syndrome and primary biliary cirrhosis (prevalence 10-20%).



Picture 5: *SSc, patient attempting to make a fist.*

Anti- Scl-70 highly specific for Scleroderma

EliA™ Scl-70 and EliA™ CENP Antigens

In 1986, the Scl-70 antigen was identified as topoisomerase 1, which catalyzes the breakage/rejoining of single-stranded DNA and relaxes supercoiled DNA in vitro. Antibodies to this enzyme in SSc patients recognise its active site and there is a strong suggestion that anti-topoisomerase antibodies (including anti Scl-70) have a role in disease progression and outcome.

The most important centromere antigen is CENP-B which is recognised by virtually all sera containing anti-centromere antibodies. Antibodies to CENP-A and CENP-C are usually cross-reacting as each of these antigens shares an epitope with CENP-B. The autoimmune response to CENP is almost always polyvalent and against all 3 antigens, therefore testing for antibodies to CENP-B is sufficient.

EliA CENP wells are coated with human recombinant CENP-B produced in eukaryotic cells using the Baculovirus/insect cell system.

Normal Range and Measuring Range

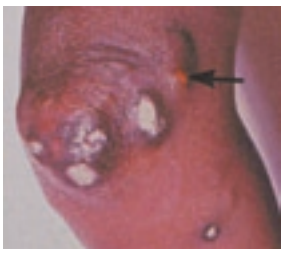
Studies to determine the normal range utilised serum from a large number of subjects. For EliA Scl-70 and EliA CENP, the following values were obtained.

	EliA Scl-70	EliA CENP
Normal Range		
Negative	<7 EliA U/ml	<7 EliA U/ml
Equivocal	7–10 EliA U/ml	7–10 EliA U/ml
Positive	>10 EliA U/ml	>10 EliA U/ml
Measuring Range ImmunoCAP 100	0.3– ≥320 EliA U/ml	0.3– ≥240 EliA U/ml
Measuring Range ImmunoCAP 100	0.4– ≥320 EliA U/ml	0.4– ≥240 EliA U/ml

Centromere antibodies have high value as prognostic indicators.

To guarantee a high consistency in results, the EliA system uses lot-specific conversion factors to calculate EliA U/ml from the original fluorescence response units. Therefore the upper limit of the measuring range for EliA assays may vary from lot to lot.

Jo-1



Picture 6: *Dermatomyositis, calcification*

Jo-1 antibodies are found as marker antibodies in dermatomyositis/polymyositis with a prevalence of about 30% but also in polymyositis overlap syndrome. They are associated with interstitial pneumonitis (in the context of myositis) and occur in a smaller proportion of children with myositis than of adults. Patients with Jo-1 antibodies tend to have a severe form of the disease with poor prognosis and a tendency to relapse. Levels of antibodies to Jo-1 appear to vary in proportion to disease activity so may indicate success of treatment or relapse. Antibodies to Ro52 frequently occur in conjunction with anti-Jo-1 antibodies in myositis patients.

EliA™ Jo-1 Antigen

- **Human recombinant antigen produced in the eukaryotic baculoviurs/insect cell system to ensure identical immunogenicity to native human form.**

Jo-1 is synonymous with histidyl–tRNA synthetase, a cytoplasmic enzyme which catalyses the esterification of histidine to its cognate tRNA. Anti-Jo-1 sera do not recognise other aminoacyl-tRNA synthetases but are specific for histidyl-tRNA synthetases from higher eukaryotes and react with highest affinity with the human enzyme. The EliA Jo-1 wells are coated with human recombinant histidyl-tRNA synthetase produced in eukaryotic cells using the Baculovirus/insect cell system.

Normal Range and Measuring Range

Studies to determine the normal range utilised serum from a large number of subjects. For EliA Jo-1, the following values were obtained.

	EliA Jo-1
Normal Range	
Negative	<7 EliA U/ml
Equivocal	7–10 EliA U/ml
Positive	>10 EliA U/ml
Measuring Range	0.3– ≥240 EliA U/ml

To guarantee a high consistency in results, the EliA system uses lot-specific conversion factors to calculate EliA U/ml from the original fluorescence response units. Therefore the upper limit of the measuring range for EliA assays may vary from lot to lot.

Performance using International Reference Preparations

IgG levels calibrated against International Reference Preparation (IRP) 67/86 from World Health Organization

The performance of the EliA ANA assays were checked with the international reference preparations from the Centers for Disease Control and Protection (CDC). The results are shown in Table 3. CDC5 has Sm and histone antibodies but not RNP antibodies as the target but is found positive in EliA U1RNP. Detailed investigation using the single antigens U1RNP 70kDa, A and C as well as SmD and B/B' showed that this is due to the well known cross reaction of antibodies to SmB/B' with those to RNP A and C. CDC10 shows additional Ro activity which is due to Ro52 antibodies that are known to frequently occur together with those to Jo-1 and indicate the development of secondary Sjögren's syndrome in myositis patients. However, the definition of CDC10 did not include a check for Ro52 antibodies.

CDC Sera	Target	EliA Sm	EliA U1RNP	EliA RNP70	EliA Ro	EliA La	EliA Scl-70	EliA CENP	EliA Jo-1
CDC1	dsDNA, weak Sm	+/-	-	-	-	-	-	-	-
CDC 2	La, weak Ro	-	-	-	+	+	-	-	-
CDC 3	Weak Sm, U1RNP, Ro, La	+/-	+	+	+	+	-	-	-
CDC 4	U1RNP	-	+	+	-	-	-	-	-
CDC 5	Sm	+	+	+/-	-	-	-	-	-
CDC 6	Nucleolar	-	-	-	-	-	-	-	-
CDC 7	SS-A/Ro	-	-	-	+	-	-	-	-
CDC 8	Centromere	-	-	-	-	-	-	+	-
CDC 9	Scl-70	-	-	-	-	-	+	-	-
CDC 10	Jo-1	-	-	-	+	-	-	-	+

Table 3: *Performance of EliA ANA assays with CDC serum panel*

The performance was also checked with the sera panel from the Association of Medical Laboratory Immunologists (AMLI).

AMLI Sample	Target	EliA Sm	EliA U1RNP	EliA RNP70	EliA Ro	EliA La	EliA Scl-70	EliA CENP	EliA Jo-1
Member A	CENP	-	-	-	-	-	-	+	-
Member B	Scl-70	-	-	-	-	-	+	-	-
Member D	U1RNP	-	+	+	-	-	-	-	-
Member E	Ro52/60	-	-	-	+	-	-	-	-
Member F	Jo-1, Ro	-	-	-	+	-	-	-	+
Member G	La, Ro	-	-	-	+	+	-	-	-
Member I	Sm, SmB,B', RNP70, C, dsDNA	+	+	+	-	-	-	-	-
Member J	dsDNA, Ro	-	-	-	+	-	-	-	-
Member K	Neg	-	-	-	-	-	-	-	-
Member L	Neg	-	-	-	-	-	-	-	-

Table 4: *Performance of EliA ANA assays with AMLI serum panel*

The results in Table 4 show that all targets are met exactly.

Technical Data

- **Products** — EliA™ Sm, EliA™ U1RNP, EliA™ RNP70, EliA™ Ro, EliA™ La, EliA™ Scl-70, EliA™ CENP, EliA™ Jo-1
- **Antigens** — Native purified SmD, human recombinant U1RNP (70kDa, A, C), Ro (60kDa, 52kDa), La, Scl-70, Centromere B and Jo-1 proteins
- **Sample Material** — Serum, Plasma (EDTA, citrate, heparin)
- **Dilution** — 1:100 (automated)
- **Reproducibility in % – ImmunoCAP 100**
  (for details see Directions For Use)

		EliA Sm	EliA U1RNP	EliA RNP70	EliA Ro	EliA La	EliA Scl-70	EliA CENP	EliA Jo-1
Intra-run	Low	3.5	2.7	6.8	2.1	5.3	2.6	2.6	2.7
	Medium	2.9	5.1	5.4	3.2	4.7	3.1	3.3	3.6
	high	3.4	3.0	4.1	4.9	5.1	2.4	3.0	2.3
Inter-run	Low	1.8	2.5	1.4	2.9	2.8	3.0	3.5	3.8
	Medium	1.6	2.3	4.9	2.5	4.4	3.2	3.4	4.9
	high	1.9	4.4	4.7	1.5	2.8	4.4	4.0	5.4

- **Reproducibility in % – ImmunoCAP 250**
  (for details see Directions For Use)

		EliA Sm	EliA U1RNP	EliA RNP70	EliA Ro	EliA La	EliA Scl-70	EliA CENP	EliA Jo-1
Intra-run	Low	5.2	6.0	4.9	5.3	6.7	8.8	9.3	5.4
	Medium	4.9	5.4	8.0	3.3	6.4	4.5	3.1	4.9
	high	5.7	5.3	4.9	3.5	6.2	4.9	5.4	5.3
Inter-run	Low	5.2	7.2	5.7	4.0	4.9	6.0	6.9	5.9
	Medium	4.2	6.8	6.2	3.9	4.7	4.9	3.8	2.1
	high	3.9	4.3	6.5	4.2	6.4	2.5	3.4	4.7

High Quality in every Respect

A company designed to ensure high quality

In our purpose-built laboratory, the Biotechnikum, all departments from research to development and production are under the same roof. The state-of-the-art concept allows complete line clearance after every production step to assure highest quality and consistency in production. A number of highly sophisticated technical systems including ultra pure air supply for the production area and USP23 pharmaceutical standard water supply facilitate the achievement of our quality goals.

Setting the quality standard of antigens

High purity and correct three-dimensional structure are the prerequisites for antigens used in reliable autoantibody assays. The best, but not the easiest way to meet these requirements is to use human recombinant antigens expressed in a eukaryotic system. Most of our antigens are produced in the Baculovirus/insect cell system which yields very pure antigens of high immunogenicity to ensure assays of excellent clinical sensitivity and specificity. Using high volume fermentation of the cells and optimised scale-up methods in protein purification, we are able to produce huge amounts of antigen in one batch and achieve a high lot-to-lot consistency in results.

Our competence is your advantage

As specialists in autoimmunity, we are happy to support you with all our expertise not only technically but also scientifically and economically. As our customer, you can send samples to our reference laboratory to find explanations for atypical or questionable results. Our scientific support includes literature support, international Phadia symposia, sponsoring of the European Autoimmunity Standardisation Initiative (EASI) and opinion leader networking. For commercial laboratories, we offer education programmes to train and support their customers.

EliA™

Excellence in Autoimmunity

Our Strength for Your Success

Ordering Information

	Package size	Article No.
EliA™ Sm Well	4 x 12	14-5502-01
EliA™ U1RNP Well	4 x 12	14-5501-01
EliA™ RNP70 Well	4 x 12	14-5511-01
EliA™ Ro Well	4 x 12	14-5503-01
EliA™ La Well	4 x 12	14-5504-01
EliA™ Scl-70 Well	2 x 12	14-5506-01
EliA™ CENP Well	2 x 12	14-5505-01
EliA™ Jo-1 Well	2 x 12	14-5507-01
EliA™ Controls		
EliA™ ANA Positive Control 100	6 vials	83-1038-01
EliA™ ANA Positive Control 250	6 vials	83-1033-01
EliA™ IgG/IgM/IgA Negative Control 100	6 vials	83-1042-01
EliA™ IgG/IgM/IgA Negative Control 250	6 vials	83-1037-01
EliA™ IgG Calibrator Well	4 x 12	14-5509-01
EliA™ on ImmunoCAP™ 100 Reagents		
EliA™ IgG Conjugate	6 x 48	83-1002-01
EliA™ IgG Conjugate	2 x 48	83-1005-01
EliA™ IgG Calibrator	6 vials	83-1000-01
EliA™ IgG Curve Control	6 vials	83-1001-01
EliA™ on ImmunoCAP™ 250 Reagents		
EliA™ IgG Conjugate 50	6 x 50	83-1017-01
EliA™ IgG Conjugate 200	6 x 200	83-1018-01
EliA™ IgG Calibrator Strips	5 strips	83-1015-01
EliA™ IgG Curve Control Strips	5 strips	83-1016-01

For general reagents, please refer to the Phadia product catalogue.

Order No. 91 51 520 Freiburg 07/2007

Phadia

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