K092399

JUL - 1 2010

510(k) PREMARKET NOTIFICATION

ORGENTEC Anti- Mutated Citrullinated Vimentin IgG EIA

(a) The device name, including the trade name or proprietary name and the common name of the device.

TRADE NAME: Anti-MCV® (Anti- Mutated Citrullinated Vimentin (MCV) EIA)

COMMON NAME: Rheumatoid factor immunological test system

Measurand:

Anti- Mutated Citrullinated Vimentin (MCV)

Type of Test:

Semi-Quantitative Enzyme immunoassay

(b) The establishment registration number, if applicable, of the owner or operator submitting the Premarket Notification submission.

MANUFACTURER: ORGENTEC Diagnostika GmbH
Carl-Zeiss-Str. 49
55129 Mainz
Germany

Establishment Registration Number: 3003232042

(c) The class in which the device has been put under section 513 of the Act and, if known, its appropriate panel; or, if the owner or operator determines that the device has not been classified under this section, a statement of that determination and the basis for the person's determination that the device is not so classified.

Based upon a review of the Classification of Devices section 21 CFR, **866.5775** Rheumatoid factor immunological test system of the type manufactured by Orgentec Diagnostika have been categorized as Class II medical devices for the Immunology Panel, as **Product Code NHX.**

Indication(s) for use:

Anti-MCV® is an indirect solid phase enzyme immunoassay (ELISA) for the qualitative and semi-quantitative measurement of IgG class autoantibodies against mutated citrullinated vimentin (MCV) in human serum. The assay is intended for in vitro

diagnostic use only as an aid in the diagnosis of Rheumatoid Arthritis (RA) in conjunction with other laboratory and clinical findings.

(d) Action taken by the person required to register to comply with the requirements of the Act under section 514 for performance standards.

This device will comply with all performance standards developed for this type of product.

(e) Proposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for use.

Draft labeling is enclosed as APPENDIX 2. APPENDIX 3 contains the proposed package insert for the Anti-MCV® Test.

(f) A statement indicating the device is similar to and/or different from other products of comparable type in commercial distribution.

The ORGENTEC Anti- Mutated Citrullinated Vimentin (MCV) IgG EIA has been compared to the Immunoscan RA anti-CCP Test Kit (Predicate Device) and data demonstrating substantial equivalence is enclosed. The manufacturer of the predicate device is Eurodiagnostica, Malmo, Sweden. The predicate device has been assigned FDA 510(k) number **K052133**.

Substantial Equivalence Information:

Rheumatoid arthritis (RA) is the most common inflammatory disease of the joints. The disease is caused by an inflammatory reaction that leads to increasing joint damage, occupational disability and premature invalidity. About 0.5 to 1 percent of the population is affected. Contrary to common belief, RA is a serious disease that affects people at all ages. In most cases it becomes manifest between the age of 30 and 50. Children and young persons can be affected as well. RA is not curable, but in many patients it is easily controlled and brought to a halt. The earlier the diagnosis is made and treatment begins, the better its progression can be slowed or even stopped. The goal for the treatment of rheumatoid arthritis today is early detection and initiation of the earliest possible effective treatment.

RA is an autoimmune disease. The trigger for this disease remains unknown. Infection by viruses or bacteria could play a role in its inception. It is highly probable that a hereditary predisposition plays an important role in this disease. It has also been demonstrated that smokers are at higher risk.
Diagnosis of RA is based on clinical findings according to the ACR criteria and on laboratory tests. Of special importance is the detection of disease-specific autoantibodies: rheumatoid factors and anti-citrullinated protein / peptide antibodies (ACPA). Determination of RF is a well established method and until now the only autoantibody laboratory parameter included in the ACR criteria. The sensitivity of RF for

RA-Diagnosis is 50 -90 % and the specificity is 50 -95 %. False positive results commonly occur in the setting of chronic infections, malignancies and other rheumatic diseases. RF is detected in the sera of 1-4 % of healthy young persons and in a high percentage of elderly persons without RA.

One of the most important serological discoveries in rheumatology in recent years has been the characterization of autoantigens in RA containing the amino acid citrulline. Citrullination is a posttranslational modification that occurs naturally during inflammation, apoptosis and keratinization. Several citrullinated proteins have been found in RA synovium and citrullinated epitopes have been identified as targets of highly RA-specific autoantibodies.

ELISA-tests using synthetic cyclic citrullinated peptides (CCP) have improved the specificity of detection of RA-autoantibodies without changing the sensitivity compared to RF. Several studies have now shown that anti-CCP antibodies are not only highly specific, but also of high predictive value for an erosive course of the disease and are thus of prognostic value.

Citrullinated vimentin is present in synovial fluid and autoantibodies directed against it are detectable in RA synovium. The most recent studies have shown that both citrullination and mutation can influence the antigenicity of vimentin. An ELISA based on mutated citrullinated vimentin (MCV) (Patented) has been commercially available for the diagnosis of rheumatoid arthritis for some time and has about the same diagnostic sensitivity and specificity as anti-CCP antibodies.

ACPA, such as anti-CCP and anti-MCV are associated with known genetic and epidemiologic risk factors for RA and therefore identify a population of RA patients with more severe, erosive joint disease that is at high risk for rapid joint destruction. The ACPA-assay may be especially valuable in predicting RA in patients who are RF-negative but nevertheless have a high probability of RA. When used in the identification of patients potentially developing RA among those presenting with early and undifferentiated symptoms, in a high risk population (rather than screening the entire population) the prevalence of the disease will be high. ACPA are strongly associated with an increased risk of developing RA in healthy individuals and are detectable in the blood of healthy persons prior to clinical manifestation of RA.

Substantial Equivalence Summary

	Immunoscan Anti-CCP IgG Antibody test kit	ORGENTEC Anti-MCV IgG EIA
Intended Use	The Immunoscan RA anti-CCP test kit is an enzyme-linked immunosorbent assay (ELISA) for qualitative detection and semi-quantitation of IgG antibodies to Cyclic Citrullinated Peptide (CCP) in human sera. The assay is used to detect antibodies in a single serum specimen. The results of the assay are to be used as an aid to the diagnosis of Rheumatoid Arthritis (RA) in conjunction with other laboratory and clinical findings. The analysis should be performed by trained laboratory professionals.	Anti-MCV® is an indirect solid phase enzyme immunoassay (ELISA) for the qualitative and semi-quantitative measurement of IgG class autoantibodies against mutated citrullinated vimentin (MCV) in human serum. The assay is intended for in vitro diagnostic use only as an aid in the diagnosis of Rheumatoid Arthritis (RA) in conjunction with other laboratory and clinical findings.
Test kit composition	Microplate 5 calibrators Reference Control Positive Control Negative Control Enzyme conjugate Dilution Buffer TMB substrate Stop solution (hydrochloric acid) Wash buffer	Microplate 6 calibrators Positive Control Negative Control Enzyme conjugate Sample Buffer TMB substrate solution Stop solution (hydrochloric acid) Wash buffer
Matrix	Human Serum containing sodium azide as preservative	Human Serum containing sodium azide as preservative
Controls	Negative control Positive control	Negative control Positive control
Sample material	human serum or plasma	human serum
Required sample size	10 µL of sample to be diluted 1:50 with Diluent; 100 µL prediluted sample per single determination	10 µL of sample to be diluted 1:100 with Diluent; 100 µL prediluted sample per single determination
Total	120 minutes at room	60 minutes at room

incubation time	temperature (18-25°C (64 - 77 °F)	temperature (18-28°C)
Test results	Qualitative and Semi-Quantitative	Qualitative and Semi-Quantitative
Storage	2-8 °C (35 - 46 °F)	2-8 °C (35 - 46 °F)
Type of substrate	TMB (3,3′,5,5′-Tetramethyl-benzidine)	TMB (3,3′,5,5′-Tetramethyl-benzidine)
Package size	96 tests	96 tests
Open Vial claim	30 days	30 days

(g) Where a person required to register intends to introduce into commercial distribution a device that has undergone a significant change or modification that could significantly affect the safety or effectiveness of the device, or the device is to be marketed for a new or different intended use, the Premarket notification submission must include appropriate supporting data to show that the manufacturer has considered what consequences and effects the change or modification or new use might have on the safety and effectiveness of the device.

Not applicable.

(h) Any additional information regarding the device requested by the Commissioner that is necessary for the Commissioner to make a finding as to whether or not the device is substantially equivalent to a device in commercial distribution.

Any additional information will be furnished upon request.

Performance Characteristics

1. Analytical performance:

a. Precision/Reproducibility:

Intra-Assay

The Intra-Assay reproducibility was determined by replicate (16 or 20) measurements of seven samples using the Anti-MCV® kit. The within assay precision is shown below:

Mean (U/mL)	3.2	21.8	17.3	20.2	111.0	451.6	806.2
S.D.	0.323	1.5	1.1	1.1	10.2	34.8	73.1
CV (%)	10.2	6.7	6.3	5.3	9.2	7.7	9.1
n =	20	20	20	16	16	16	16

Inter-Assay

Run-to-run precision was calculated from the results of five different runs with single determinations of each sample. Mean, S.D. and C.V. of the ten measurements is given below.

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7
Mean (U/mL)	5.0	20.1	22.7	27.0	118.8	548.1	981.5
S.D.	0.76	2.9	1.4	3.7	7.6	25.1	68.7
CV (%)	15.3	14.2	6.2	13.6	6.4	4.6	7.0
n =	5	5	5	5	5	5	5

Inter-Lot

Three lots of kits per sample were used to evaluate Inter-Lot reproducibility. The results of the testing are shown below using twelve sera of differing values run in single determination.

Sample No.	Mean [U/ml]	S.D.	CV [%]
1	6.9	0.9	13.0
2	17.2	2.5	14.4
3	20.4	1.7	8.4
4	21.9	2.2	10.2
5	27.6	2.0	7.4
6	130.4	17.1	13.1
7	150.3	7.8	5.2
8	255.1	9.4	3.7
9	255.7	27.1	10.6
10	327.0	4.8	1.5
11	652.2	120.3	18.4
12	1043.2	17.3	1.7

Inter-Laboratory

Inter-Laboratory precision was calculated for each of twenty-two samples tested in single determination with one lot by three individuals in three different laboratories.

Inter-Laboratory			
Sample No.	Mean [U/ml]	S.D.	CV [%]
1	4.6	0.5	11.2
2	6.9	1.0	14.5
3	4.1	0.6	13.3
4	5.5	0.8	14.9
5	19.9	0.6	2.8
6	18.5	0.6	3.1
7	39.5	4.0	10.2
8	37.3	3.8	10.2
9	78.4	3.8	4.8
10	73.3	2.5	3.4
11	141.6	2.9	2.8
12	138.7	3.8	2.7
13	173.8	8.0	4.6
14	171.8	18.4	10.7
15	234.6	17.3	7.4
16	242.4	28.7	11.8
17	222.4	20.9	9.4

18	214.1	17.0	7.9
19	266.6	21.8	8.2
20	245.4	5.6	2.3
21	487.1	11.9	2.4
22	538.3	69.1	12.8

b. Linearity:

Four patient samples containing high levels of antibody were serially diluted in buffer to demonstrate the upper end of linearity and throughout the dynamic range of the assay. The calculated values together with the recovery and the linear regression coefficient (R^2) are shown in the table below. The reportable range of the assay is 3.0 to 900 U/mL

	Sample 1	Sample 2	Sample 3	Sample 4
Concentration U/mL	882.8	932.1	727.9	901.3
Regression R^2	0.9963	0.9993	0.9999	0.9971
Average % Recovery	90	102	97	106
Range of % Recovery	81-100	93-109	84-100	93-108

The results show a statistically significant coefficient for the linear reaction throughout the full dynamic range of the assay; the actual values from t-test do not exceed the upper limit from t-test table.

The ORGENTEC Anti-MCV® ELISA is linear throughout the complete measuring range.

c. Expected values (controls, calibrators, or methods):

EXPECTED VALUES

A series of 209 assumed normal blood donor samples ages 18 to 69 years were collected from various blood banks These 209 samples were tested in the Orgentec Anti-MCV® assay to determine a normal range and cut-off for the assay.

The combined mean concentration of Anti-MCV® antibodies was 5.6 U/ml. The mean+2SD was 12.8 U/mL, and.mean+3SD = 16.5 U/mL.

Based on these results the cut-off was determined to be $\geq$ 20 U/ml.

At a cut-off of $\geq$ 20 U/ml, 1 samples was positive for a specificity of 99.5%.

d. Detection limit:

The reportable range is 3 to 900 U/mL.

e. Analytical specificity:

Interferences

Interference due to bilirubin, hemolysis and lipemia was evaluated using a negative serum, a low positive serum and a high positive serum spiked with the respective interfering substance

in increasing concentrations. Hemolysis up to 1000 mg/dL, bilirubin up to 40 mg/dL, and lipemia (i.e. triglyceride concentration) up to 3000 mg/dL in human serum do not interfere with Anti-MCV® ELISA results.

Cross-reactivity

A series of patient samples from other potentially cross-reacting and similar symptoms to Rheumatoid Arthritis were evaluated for reactivity in the Anti-MCV® assay. 1.9 % of these samples were found positive.

The results of the testing are summarized below.

Condition	Total No.	Positives No.	Positives %	**Clinical Specificity %**
Blood donors	443	4	0.9%	99.1%
Psoriasis Arthritis	10	0	0.0%	100.0%
Juvenile Arthritis	15	0	0.0%	100.0%
Scleroderma	8	0	0.0%	100.0%
Sicca Symptomatic	6	0	0.0%	100.0%
Sjögren Syndrome	50	2	4.0%	96.0%
UCTD	25	1	4.0%	96.0%
MCTD	6	0	0.0%	100.0%
SLE	97	3	3.1%	96.9%
APS	20	0	0.0%	100.0%
Celiac Disease	75	1	1.3%	98.7%
Morbus Crohn	1	0	0.0%	100.0%
Microscopic Polyangiitis	30	2	6.7%	93.3%
Morbus Wegener/Vasculitis	7	0	0.0%	100.0%
Polymyositis/Dermatomyositis	3	0	0.0%	100.0%
Thyroiditis	104	3	2.9%	97.1%
div. Infectious Diseases	25	0	0.0%	100.0%
Diabetes Mellitus	40	2	5.0%	95.0%
Non-RA:	965	18	1.9%	**98.1%**

f. Assay cut-off:

cut-off of ≥ 20 U/ml is positive

Comparison/Clinical studies:

a. Method comparison with predicate device / Clinical comparison:

Studies were performed to evaluate the sensitivity and specificity of the Anti-MCV® (ELISA) test when compared to the predicate assay Anti-CCP assay using a mix of clinically diagnosed Rheumatoid Arthritis disease state samples and a presumed normal asymptomatic blood bank population plus other arthritic and autoimmune patient samples obtained from hospital labs and autoimmune clinics.

Specificity can be defined as the ability of a test to give a negative result for "normal" and control disease sera. The specificity performance of the ORGENTEC Anti-MCV® assay was

established using 234 "presumed normal" sera obtained from blood donor centers age 24 to 82 years, 522 other samples from patients with arthritic and autoimmune disease conditions, obtained from a variety of clinical sources (hospitals and autoimmune clinics) age 2 to 92 years. The samples collectively included 166 males and 590 females.

Sensitivity can be defined as the ability of a test to give a positive result for sera from patients diagnosed with an autoimmune disorder. The sensitivity performance of the ORGENTEC Anti-MCV® assay was established using four hundred and ninety samples from clinically diagnosed patients as having Rheumatoid Arthritis disease that were obtained from a variety of clinical sources (hospitals and autoimmune clinics). The patients collectively included 124 males and 366 females. The age ranged from 19 to 92 years.

The results were calculated for each sample from a calibration curve on the basis of six calibrators tested. Quantitative values above or equal to 20 U/ml were considered positive, values below 20 U/ml were considered negative.

Five hundred and fifty five (555) sera were tested by the ORGENTEC Anti-MCV® ELISA and by the commercially available Anti-CCP IgG ELISA. The quantitative results were calculated from a calibration curve on the basis of tested calibrators. In the ORGENTEC Anti-MCV® assay quantitative values above or equal to 20 U/ml were considered positive, values below 20 U/ml were considered negative. In the Anti-CCP IgG assay quantitative values above or equal 25 U/ml were considered positive, values below 25 U/ml were considered negative.

Based on clinical diagnosis, three hundred ninety-eight of the 490 Rheumatoid Arthritis disease diagnosed sera were positive in the ORGENTEC Anti-MCV® assay and ninty-two tested as negative, thus yielding a clinical diagnostic sensitivity of 81.2%.
Note that the predicate assay also missed many of the same specimens. This data is consistent with reported data of sensitivities ranging from 69 % to 82 % for commercial Anti-MCV IgG assay for the diagnosis and follow up of RA Disease patients (Table in Egerer et al., Deutsches Ärzteblatt International Dtsch Arztebl Int 2009; 106 (10):159–63).

A summary analysis of the results are shown in the following Tables:

			Comparative Method		
			Pos	Neg	
	ORGENTEC Assay	Pos	231	10	
		Neg	9	305	
			240	315	555
Positive Percent Agreement:	**96.3%**		C.I. (95%) = 93.0 - 98.3%		
Negative Percent Agreement:	**96.8%**		C.I. (95%) = 94.2 - 98.5%		
Overall Agreement:	**96.6%**		C.I. (95%) = 94.7 - 97.9%		

			Clinical Diagnosis		
			Pos	Neg	
	ORGENTEC Assay	Pos	398	15	
		Neg	92	741	
			490	756	1246
Clinical Sensitivity:	**81.2%**		C.I. (95%) = 77.8 - 84.7%		
Clinical Specificity:	**98.0%**		C.I. (95%) = 96.7 - 98.9%		
Clinical Agreement:	**91.5%**		C.I. (95%) = 89.7 - 92.9%		

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food & Drug Administration
10903 New Hampshire Avenue
Building 66
Silver Spring, MD 20993

Orgentec Diagnostica GmbH
c/o Mr. Gary Lehnus
150 Cherry Lane Road
East Stroudsburg, PA 18301

JUL 01 2010

Re: k092399
Trade/Device Name: Anti-mutated Citrullinated Vimentin IgG EIA
Regulation Number: 21 CFR 866.5775
Regulation Name: Rheumatoid factor immunological test system
Regulatory Class: Class II
Product Code: OQZ
Dated: June 25, 2010
Received: July 1, 2010

Dear Mr. Lehnus:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act

or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

for Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indications for Use Form

510(k) Number (if known): **K092399**

Device Name: **Anti-MCV® (Anti- Mutated Citrullinated Vimentin) EIA**

Indications for Use:

Anti-MCV® is an indirect solid phase enzyme immunoassay (ELISA) for the qualitative and semi-quantitative measurement of IgG class auto antibodies against mutated citrullinated vimentin (MCV) in human serum. The assay is intended for in vitro diagnostic use only as an aid in the diagnosis of Rheumatoid Arthritis in conjunction with other laboratory and clinical findings.

Prescription Use ___X___ AND/OR Over-The-Counter Use ____
(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k)