August 2, 2019

Axis-Shield Diagnostics Limited
Claire Dora
Regulatory Affairs Manager
Luna Place, The Technology Park
Dundee DD2 1XA, Scotland, UK

Re: K183088
Trade/Device Name: ADVIA Centaur Erythropoietin (EPO) assay
Regulation Number: 21 CFR 864.7250
Regulation Name: Erythropoietin Assay
Regulatory Class: Class II
Product Code: GGT
Dated: July 1, 2019
Received: July 3, 2019

Dear Claire Dora:

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. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. 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. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. 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 Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

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 https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Takeesha Taylor-Bell
Chief
Division of Immunology
and Hematology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*

K183088

Device Name
ADVIA Centaur® Erythropoietin (EPO) assay

Indications for Use *(Describe)*

The ADVIA Centaur® Erythropoietin (EPO) assay is for in vitro diagnostic use in the quantitative measurement of erythropoietin in pediatric and adult human serum or plasma (K2-EDTA, lithium heparin, sodium heparin) using the ADVIA Centaur XP system. Measurement of erythropoietin is used as an aid in the diagnosis of anemias and polycythemias..

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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ADVIA Centaur Erythropoietin (EPO) Assay
510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

A. 510(k) number is: K183088

B. Date of Preparation: 08-02-2019

C. Submission correspondent:

Dr. Claire Dora
Regulatory Affairs Manager
Axis-Shield Diagnostics Ltd.
The Technology Park
Dundee
DD2 1XA,
Scotland, UK

D. Device Name:

ADVIA Centaur® Erythropoietin (EPO) Assay

E. Regulatory Information:

Classification Name: Assay, Erythropoietin
Trade Name: ADVIA Centaur® Erythropoietin (EPO) Assay
Common Name: Erythropoietin
Governing Regulation: 864.7250
Device Classification: Class II
Classification Panel: Hematology
Product Code: GGT

F. Legally marketed device to which equivalency is claimed:

Beckman Coulter Access EPO Assay (K052223)

G. Intended Use of Device:

The ADVIA Centaur® Erythropoietin (EPO) assay is for in vitro diagnostic use in the quantitative measurement of erythropoietin in pediatric and adult human serum or plasma (K2-EDTA, lithium heparin, sodium heparin) using the ADVIA Centaur XP system. Measurement of erythropoietin is used as an aid in the diagnosis of anemias and polycythemias.

H. Device Description:

Principles of the Device:

The ADVIA Centaur EPO assay is a fully automated, one-step sandwich immunoassay using direct chemiluminescent technology. The assay utilizes an acridinium-ester-labeled monoclonal mouse anti-EPO antibody in the Lite Reagent. The Solid Phase consists of mouse anti-EPO monoclonal antibody-coated paramagnetic microparticles.

The ADVIA Centaur EPO reagent kit contains the following:
ADVIA Centaur EPO ReadyPack® primary reagent pack;
Lite Reagent (10.0 mL/reagent pack): monoclonal mouse anti-EPO antibody (0.5 μg/mL) labeled with DMAE acridinium conjugate reagent in buffer with bovine serum albumin, surfactant, and sodium azide (< 0.1%)
Solid Phase Reagent (24.0 mL/reagent pack): anti-EPO mouse monoclonal antibody coated streptavidin microparticles (0.30 mg/mL) in buffer with bovine serum albumin, surfactant, and preservatives
ADVIA Centaur EPO Calibrator (2.0 mL/vial): recombinant human EPO, calf serum, and preservative.

I. Comparison of Technological Characteristics:

The ADVIA Centaur EPO assay and the Beckman Coulter Access EPO Assay are both automated immunoassays for the quantitative measurement of erythropoietin in human serum and plasma.

The ADVIA Centaur System and Beckman Access share similar detection methods both utilizing chemiluminescent microparticle immunoassay (CMIA) technology.
Both assays also demonstrated substantial equivalence as described in the table below:

Comparison of the subject device with the predicate device:

Similarities:

Parameter	New Device ADVIA Centaur Erythropoietin (EPO)	Predicate Device Beckman Access EPO
Intended use	The ADVIA Centaur® Erythropoietin (EPO) assay is for in vitro diagnostic use in the quantitative measurement of erythropoietin in human serum and plasma using the ADVIA Centaur systems. Measurement of erythropoietin is used as an aid in the diagnosis of anemias and polycythemias.	The Access EPO assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of erythropoietin levels in human serum and plasma (heparin) using the Access Immunoassay Systems. This assay is intended as an aid in the diagnosis of anemias and polycythemias. With the advent of the administration of recombinant erythropoietin as a biologic therapy to increase red blood cell mass, an erythropoietin assay may be used also to aid in the prediction and monitoring of response to recombinant erythropoietin treatment of anemias.
Assay technology	Chemiluminescent microparticle immunoassay (CMIA)	Chemiluminescent microparticle immunoassay (CMIA)
Calibration range	Up to 750 mIU/mL	Up to 750 mIU/mL
Storage conditions	Reagent, calibrator and control pack must be stored at intended storage (2-8°C)	Reagent and calibrator pack must be stored at intended storage (2-10°C)
Open stability	Calibrators are stable opened for 90 days	Calibrators are stable at 2-10°C for 90 days after initial use.

Differences:

Parameter	New Device ADVIA Centaur Erythropoietin (EPO)	Predicate Device Beckman Access EPO
Substrate / signal generation	Acridinium tracer	Alkaline phosphatase
Conjugate antibody	Monoclonal mouse anti-EPO antibody	Polyclonal chicken anti-recombinant mouse EPO antibody
Calibration	2-point calibration using 2 level adjustors	6 level calibration
Calibration frequency	14 days	28 days
Specimen type	Human Serum and plasma (K2-EDTA, lithium heparin, sodium heparin)	Serum, Plasma (Heparin)
Expected Values – Adults (>21yrs)	5.44 – 26.25 mIU/mL	2.59 – 18.50 mIU/mL
Expected Values – Paediatrics (< 22 yrs)	Male Child (2-12yrs) : 4.13 – 25.52 Male Adolescent (13-21yrs) : 4.15 – 26.15 Female Child (2-12yrs) : 4.94 – 24.47 Female Adolescent (13-21yrs) : 4.07 – 40.30	Not reported
Sensitivity	Limit of Quantitation is 0.83 mIU/mL	Analytical Sensitivity, lowest limit of Detection: 0.6 mIU/mL

Parameter	New Device ADVIA Centaur Erythropoietin (EPO)	Predicate Device Beckman Access EPO
Linearity	0.83 – 750.00 mIU/mL	3.2 – 557.2 mIU/mL
Measureable range	0.83 – 750.00 mIU/mL	0.6 – 750 mIU/mL
Assay dilution protocol	1:10 On-board auto dilute with ADVIA Centaur Multi-Diluent 13	On-board 1:5 with Access Sample Diluent A Manual 1:5 or 1:10 with Access EPO Calibrator S0 or Access Sample Diluent A.
On-board stability	Reagents can be stored on-board for 28 days. Calibrators are stable on-board for 24 hours	Reagents: On-board not stated. Calibrators - On-board not stated.

J. Summary of Non-Clinical Performance:

The ADVIA Centaur EPO assay demonstrated substantially equivalent performance to the Beckman Coulter Access EPO assay. A summary of the non-clinical performance data included in this 510(k) submission has been presented.

Linearity

Linearity was evaluated according to the CLSI protocol EP06-A.
Three samples containing high levels of EPO were mixed with low EPO human serum. The resulting sample mixtures were assayed for EPO. The ADVIA Centaur EPO assay is linear from 0.83–750.00 mIU/mL.

Dilution Recovery

Ten samples containing high levels of EPO (618.63-986.07 mIU/mL) were diluted 1:10 (1 part sample plus 9 parts diluent) with ADVIA Centaur Multi-Diluent 13 and assayed for recovery correcting the diluted sample by the dilution factor.
In a representative study the observed percent recovery for individual samples ranged from 76 - 111%.

Measuring Interval

The ADVIA Centaur EPO assay measures erythropoietin concentrations from 0.83 –750.00 mIU/mL.

Detection Capability

The limit of blank (LoB), limit of detection (LoD), and the limit of quantitation (LoQ) were determined as described in CLSI Document EP17-A2.
The LoB is defined as the highest measurement result that is likely to be observed for a blank sample. The ADVIA Centaur EPO assay has an LoB of 0.46 mIU/mL.
The LoD is defined as the lowest concentration of EPO that can be detected with 95% probability. The ADVIA Centaur EPO assay has an LoD of 0.75 mIU/mL based on 323 determinations using 10 low level samples, and an LoB of 0.46 mIU/mL.
The LoQ is defined as the lowest concentration of EPO that can be detected at a total error of 30%. The ADVIA Centaur EPO assay has an LoQ of 0.83 mIU/mL.
Report results below the LoQ as < 0.83 mIU/mL.

High Dose Hook

Patient samples with high EPO levels can cause a paradoxical decrease in the Relative Light Units (RLUs) (high-dose hook effect). In the ADVIA Centaur EPO assay, patient samples with EPO levels as high as 114,500 mIU/mL will assay greater than 750.00 mIU/mL.

Cross-reactivity

Cross-reactivity was tested in the presence of EPO at concentrations of approximately 4 - 6 mIU/mL of EPO according to CLSI EP07-A2. Testing was performed with normal human plasma proteins, and with recombinant erythropoiesis-stimulating agents (ESAs).

The ADVIA Centaur EPO assay showed minimal cross-reactivity with normal human plasma proteins. The following normal human plasma proteins were tested

Cross-reactant	Concentration	% Cross reactivity
α-2-macroglobulin	400 mg/dL	- 0.01
Transferrin (iron-saturated)	200 mg/dL	0.00
Transferrin (non-saturated)	200 mg/dL	0.00
rh Thrombopoietin	10,000 ng/mL	- 0.10
α-1-acid glycoprotein	80 mg/dL	0.01
α-1-antitrypsin	200 mg/dL	0.00
α- and β-globulins	5 g/dL	0.000
Gamma Globulins	6 g/dL	0.000

The ESAs, epoetin alfa and darbepoetin alfa were also tested. The concentration of darbepoetin was converted using the following formula: 1ng/mL = 166 mIU/mL.[1]

Note; The cross-reactivity results of the ESAs are provided for information only and should not be used to make a therapeutic decision.

Cross-reactant	Concentration	EPO (mIU/mL)	% Cross-reactivity
Epoetin alfa	1000 mIU/mL	>750	N/A
	250 mIU/mL	72.35	27.13
	125 mIU/mL	27.59	18.46
	65 mIU/mL	18.28	21.17
Dabepoetin alfa	2075 mIU/mL (12.5 ng/mL)	152.82	7.14
	518.75 mIU/mL (3.125 ng/mL)	32.26	5.31
	259.29 mIU/mL (1.562 ng/mL)	20.84	6.22
	129.65 mIU/mL (0.781 ng/mL)	13.5	6.78

[1] Conversion from ng/mL to mIU/mL used, ng/mL x 166, this was taken from Owen & Roberts *Clinica Chimica Acta.* 412 (2011) 480-482

Interference

Potential interference in the ADVIA Centaur EPO assay from hemoglobin, bilirubin, and lipemia, is designed to be ≤ 10% at EPO concentrations of approximately 4 - 6 mIU/mL and 25 - 35 mIU/mL.

Interfering substances at the levels indicated in the table below were tested as described in CLSI Document EP07-A227 using the ADVIA Centaur EPO assay.

Serum specimens that are...	Have an insignificant effect on the assay up to...
hemolyzed	500 mg/dL (0.31 mmol/L) of haemoglobin
icteric	60 mg/dL (1026 µmol/L) of unconjugated bilirubin
icteric	40 mg/dL (475 µmol/L) of conjugated bilirubin
lipemic	3000 mg/dL (34.0 mmol/L) of lipemia (Intralipid)

Two levels of EPO were tested with each of the following substances at the levels indicated, and caused no significant interference in the ADVIA Centaur EPO assay at EPO concentrations of approximately 4 - 6 mIU/mL and 25 - 35 mIU/mL.

Substances	Concentrations
Acetaminophen	14 mg/dL (927 µmol/L) [a]
Acetylsalicyclic acid	50 mg/dL (2.8 mmol/L)
Biotin	100 mg/dL (4.1 mmol/L)
Cholesterol	500 mg/dL (12.95 mmol/L)
EPO Soluble Receptor	15 ng/mL [a]
Heparin	8000 U/dL
Human Gamma Globulins	4.9 g/dL [b]
Ibuprofen	40 mg/dL (1942 µmol/L)
Multivitamin	0.2% (therapeutic level)
Protein Albumin (human)	6 g/dL (60 g/L) [a]
Rheumatoid Factor	200 IU/mL
Silwet L720	0.2 mg/dL
Total Protein	12 g/dL (120 g/L)
Triglycerides	1000 mg/dL (11.3 mmol/L)

[a]concentration-response curve performed to determine non-interfering levels (See detailed study below)

[b]concentration determined by spiking and recovery method

When targeted concentrations of interfering substances caused >10% change in EPO values, further investigation was performed.

Substances	**EPO Concentrations Tested**	**Level ≤10% change was observed**	**Level >10% change was observed**
Acetaminophen	4 – 6 mIU/mL	< 14 mg/dL (927µmol/L)	> 18 mg/dL (1192µmol/L)
	25 – 35 mIU/mL	20 mg/dL (1324 µmol/L)	--
Albumin (human)	4 – 6 mIU/mL	< 6.0 g/dL (60 g/L)	> 6.8 g/dL (68 g/L)
	25 – 35 mIU/mL	65.2 mg/mL	--
EPO soluble receptor	4 – 6 mIU/mL	< 25.00 ng/dL	> 31.25 ng/dL
	25 – 35 mIU/mL	< 15.61 ng/mL	> 18.75 ng/mL
Human gamma globulins (IgG)	4 – 6 mIU/mL	7.2 g/dL	--
	25 – 35 mIU/mL	4.9 g/dL	6.7 g/dL

Assay results obtained at individual laboratories may vary from the data presented.

Precision

Seven pooled serum samples were prepared with EPO concentrations spanning the measuring interval. Samples were tested in replicates of 2, in 2 runs per day, over 20 days, yielding 80 observations per sample. One ADVIA Centaur XP system and 3 reagent lots were used.

Representative data from the study is shown in the following table:

			Repeatability (Within-Run)		Within-Lab (Total)	
Specimen	**N**	**Mean (mIU/mL)**	**SD (mIU/mL)**	**CV (%)**	**SD (mIU/mL)**	**CV (%)**
Sample 1	80	1.69	0.08	4.8	0.14	8.4
Sample 2	80	4.51	0.13	2.9	0.23	5.0
Sample 3	80	9.30	0.25	2.6	0.33	3.6
Sample 4	80	25.16	0.54	2.2	1.00	4.0
Sample 5	80	94.30	1.82	1.9	3.22	3.4
Sample 6	80	220.25	3.69	1.7	7.03	3.2
Sample 7	80	579.41	9.20	1.6	15.17	2.6

Specimen Collection Comparison

The ADVIA Centaur EPO assay was evaluated using different human serum and plasma matrices. The assay is designed to have a correlation coefficient (r) ≥ 0.95, a slope of 0.90–1.10, and an intercept ± 1.00 mIU/mL for alternate tube types (y) versus human serum (x). A specimen collection study was performed with serum EPO values ranging from 4.39 - 707.81 mIU/mL.

Passing-Bablok regression and a Pearson coefficient analysis were performed and no significant difference between tube types was observed. The following results were obtained:

Human Serum (x) Vs	**n**	**Slope**	**Intercept (mIU/mL)**	**r**
K2-EDTA (y)	65	0.97	-0.30	1.00
Lithium Heparin (y)	65	1.00	-0.27	0.99
Sodium Heparin	65	0.98	-0.33	0.99
Plasma Separator Tube	65	0.99	-0.33	1.00
Serum Separator Tube	65	1.02	-0.20	0.99

K. Summary of Clinical Performance:

The ADVIA Centaur EPO assay demonstrated substantially equivalent performance to the predicate as indicated by reference intervals (expected values) and a method comparison.

Method Comparison

A total of 216 human serum samples in the range of 3.29 – 691.60 mIU/mL were tested on the Centaur XP system vs. the predicate following CLSI EP09-A3.

The relationship of the ADVIA Centaur EPO assay (y) and a comparator EPO assay (x) is described using Passing-Bablok regression and a Pearson coefficient using the ADVIA Centaur XP system. Data from the study is shown below:

ADVIA Centaur EPO (y) = 0.99 (x) + 0.81 mIU/mL (intercept), r = 0.99.

A second method comparison was performed with a total of 100 human serum samples from US population in the range of 4.45 – 407.74 mIU/mL were tested on the Centaur EPO assay and a comparator EPO assay following CLSI EP09-A3.

The relationship of the ADVIA Centaur EPO assay (y) and the comparator EPO assay (x) is described using Passing-Bablok regression and a Pearson coefficient using the ADVIA Centaur XP system. Data from the study is shown below:

ADVIA Centaur EPO (y) = 1.07 (x) + 0.00 mIU/mL (intercept), r = 1.00.

A third mutli-site study was performed 3 sites, 2 within Europe and 1 within the US tested a total of 327 human serum samples (≥ 100 samples per site) in the range of 3.55 – 596.81 mIU/mL were tested on the Centaur EPO assay and a comparator EPO assay.

The relationship of the ADVIA Centaur EPO assay (y) and the comparator EPO assay (x) is described using Passing-Bablok regression and a Pearson coefficient using the ADVIA Centaur XP system. Data from the study is shown below:

ADVIA Centaur EPO (y) = 1.01 (x) + 0.36 mIU/mL (intercept), r = 0.99.

Expected Values

The ADVIA Centaur EPO assay results were obtained on 251 apparently healthy subjects, males (n=128) and females (n=123), older than 21 years of age using the ADVIA Centaur XP system. Samples were collected between 7:30 am and 12 noon from individuals with normal hematocrit and hemoglobin levels. Smokers, pregnant women, people living at high altitude or having donated blood within 60 days were excluded.

The reference intervals in the following table were calculated non-parametrically according to EP28-A3.

ADVIA Centaur EPO Reference Ranges

Gender	N	Mean (mIU/mL)	Median (mIU/mL)	95% CI of Median (mIU/mL)	95% Reference Range (mIU/mL)
Combined Male and Female	251	11.20	10.08	9.43 – 10.52	5.44 –26.25

ADVIA Centaur EPO Pediatric Ranges

The ADVIA Centaur EPO assay results were obtained on 266 apparently healthy children (2 to <13 years) and adolescents (13 to <22 years) using the ADVIA Centaur XP system. Samples were collected 6:00 am and 12 noon from individuals who were of normal weight and height for their age, and were without known diseases.

The reference intervals are presented in the table below and were calculated by means of robust biweight estimators.[2]

ADVIA Centaur EPO Pediatric Ranges

Gender	Age	N	Mean (mIU/mL)	Median (mIU/mL)	95% CI of Median (mIU/mL)	95% Reference Range (mIU/mL)
Male Child	2-12	72	9.80	9.21	8.14-9.89	4.13-25.52
Male Adolescent	13-21	60	10.44	9.30	8.18-10.40	4.15-26.15
Female Child	2-12	74	10.62	9.02	8.20-9.97	4.94-24.47
Female Adolescent	13-21	60	11.96	8.50	8.04-10.78	4.07-40.30

As with all in vitro diagnostic assays, each laboratory should determine its own reference range(s) for the diagnostic evaluation of patient results. Consider these values as guidelines only.

[2] Horn P, Pesce A. *Reference Intervals – A User's Guide.* Washington DC: AACC Press; 2005

L. Standardization:

The ADVIA Centaur EPO assay is traceable to the World Health Organization (WHO) 2nd International Reference Preparation for Erythropoietin (Human, urinary derived); NIBSC code: 67/343. Assigned values for calibrators are traceable to this standard. The ADVIA Centaur EPO assay is also traceable to the 3rd World Health Organization (WHO) International Standard for Erythropoietin, recombinant, for bioassay; NIBSC code: 11/170

M. Conclusion:

Based on the performance characteristics the ADVIA Centaur EPO assay is substantially equivalent to the predicate device.