

K983203

JUL 12 1999

510(k) Summary

This summary of safety and effectiveness information has been prepared in accordance with the requirements of SMDA 1990 and 21 CFR Part 807.92.

Name: Diagnostic Products Corporation
Address: 5700 West 96th Street
Los Angeles, CA 90045

Telephone Number: (310) 645-8200
Facsimile Number: (310) 645-9999

Contact Person: Edward M. Levine, Ph.D.
Director of Clinical Affairs

Date of Preparation: June 7, 1999

Device Name
Trade: IMMULITE[®] EPO
Common: Reagent system for the determination of EPO in serum and heparinized plasma

Catalog Number: LKEPZ (50 tests), LKEP1 (100 tests)

Classification: Class III device (pre-amendment)
21CFR 864.7250

CLIA Complexity
Category: Moderate, based on previous classification of analogous tests

Manufacturer: Diagnostic Products Corporation
5700 West 96th Street
Los Angeles, CA 90045-5597

Establishment Registration
Number: DPC's Registration Number is 2017183

Substantially Equivalent
Predicate Device: Incstar's EPO-Trac ¹²⁵I RIA (K902639)

Description of the Device: IMMULITE[®] EPO is a solid-phase, two-site sequential chemiluminescent enzyme immunometric assay for use with the IMMULITE[®] Automated Immunoassay Analyzer

Intended Use of the Device:

IMMULITE[®] EPO is a solid-phase, two-site sequential chemiluminescent enzyme immunometric assay for use with the IMMULITE Automated Analyzer and designed for the quantitative measurement of erythropoietin (EPO) in serum or heparinized plasma. It is intended strictly for *in vitro* diagnostic use as an aid the diagnosis of anemias and polycythemias.

Summary and Explanation of the Test:

Erythropoietin (EPO) is a glycoprotein hormone consisting of 165 amino acids, with four complex carbohydrate chains attached to the peptide at four linkage sites. It has a molecular weight of 36,000 daltons, 40% of this attributed to the carbohydrate chains. EPO is the primary regulator of erythropoiesis, stimulating the proliferation and differentiation of erythroid precursor cells in bone marrow. In mammals, the fetal liver produces nearly all of the hormone; in adults, hepatic production drops to under 10% and renal secretion accounts for over 90%. The production site is believed to be the proximal renal tubular cells or the peritubular capillary endothelial cells of the renal cortex and outer medulla. The clearance of circulating EPO has not been fully explained, but it is accomplished, in small part, by urinary excretion, and possibly also by hepatic elimination and by uptake into target cells in bone marrow.

EPO adjusts red blood cell production to meet the tissue oxygen demand. It exerts its effect in a complex feedback system, in which renal secretion of the hormone is controlled by an oxygen sensor in the kidney that responds to the partial pressure of oxygen in blood. Under conditions of increased peripheral oxygen, EPO levels diminish. This is seen after correction of hypoxia in healthy subjects (as in descent from a high elevation) and after hypertransfusion.

Anemias may be divided into two categories with respect to EPO levels in blood: those that are primary to EPO levels and those that are secondary. Primary anemias are characterized by an increase of EPO in the blood to attempt to restore red blood cell production levels to normal. Examples of anemias in which EPO levels are elevated include iron deficiency anemia, reduction of blood flow to the kidney (as in blood loss) and hemoglobinopathies with increased affinity of hemoglobin for oxygen. The EPO production rate is seen to increase exponentially with the decrease in available oxygen and with falling hematocrit in nonrenal anemias; in the latter, EPO levels 1,000 times normal have been reported.

Anemia can be secondary to inflammation, rheumatoid arthritis, neoplasm, and chronic renal disease. The "secondary anemias" may, however, be at least partly attributable to underproduction of EPO.

A failure to produce sufficient EPO accounts for the moderate to severe anemias observed in end-stage renal disease. Decreased EPO production is attributed to destruction of renal production sites; the renal oxygen sensor may also be affected. Levels of the hormone slightly exceed the reference range at most, and are inadequate to counter the blood loss due to dialysis, shortened red blood cell life, iron and folate deficiency, impaired iron transfer to erythroid progenitor cells and other challenges faced by such patients. Anephric patients demonstrate especially low EPO levels. A few patients with chronic kidney failure, however, exhibit normal hematocrits or less serious anemia, and elevated EPO. Some of these patients have cystic kidneys or viral hepatitis; in the latter, increased EPO may have resulted from enhanced hepatic production.

Overproduction of red blood cells is called polycythemia. Polycythemias may also be divided into two categories depending on whether the condition is primary or secondary to EPO levels. In polycythemia vera, EPO levels are diminished and erythropoiesis is primary to and independent of stimulation by EPO. Variation in EPO values can be as much as tenfold for different patients with the same hematocrit.

Certain conditions may be characterized by the loss of feedback control of oxygen concentration over EPO production, causing an increase in EPO levels. These include renal cell carcinomas, in which 2% of patients demonstrate erythrocytosis, and some benign renal lesions, such as single or multiple renal cysts, renal artery stenosis and microvascular abnormalities. In addition, approximately 10% of renal transplant patients develop erythrocytosis, sometimes from autologous diseased kidney.

Secondary polycythemia is characterized by elevated EPO levels which lead to increased red blood cell mass. This condition may result from a variety of factors, including defective hemoglobin, smoking, pulmonary fibrosis, cardiac disease, tumors, and kidney stones.

When assaying EPO for the differential diagnosis of polycythemias, the possible overlap of values for secondary erythrocytosis or for polycythemia vera with those in the reference range must be considered.

Technological Comparison to Predicate:

IMMULITE[®] EPO is a solid-phase, two-site sequential chemiluminescent enzyme-labeled immunometric assay. The solid phase, a polystyrene bead enclosed within an IMMULITE Test Unit, is coated with an anti-ligand specific for EPO.

The patient sample and a ligand-labeled monoclonal anti-EPO antibody are simultaneously introduced into the Test Unit and incubated for approximately 30 minutes at 37 °C with intermittent agitation. During this time, EPO in the sample binds to the anti-ligand on the solid phase.

An alkaline phosphatase-labeled polyclonal anti-EPO antibody is introduced, and the Test Unit is incubated for another 30-minute cycle. The unbound enzyme conjugate is removed by a centrifugal wash. Substrate is then added and the Test Unit is incubated for a further 10 minutes.

The chemiluminescent substrate, a phosphate ester of adamantyl dioxetane, undergoes hydrolysis in the presence of alkaline phosphatase to yield an unstable intermediate. The continuous production of this intermediate results in the sustained emission of light, thus improving precision by providing a window for multiple readings. The bound complex – and thus also the photon output, as measured by the luminometer – is proportional to the concentration of EPO in the sample.

The Incstar's EPO-Trac ¹²⁵I RIA procedure is a competitive binding, disequilibrium radioimmunoassay which utilizes recombinant human erythropoietin for both tracer and standards. Samples are incubated with the EPO-Trac primary goat antibody (goat anti-EPO) and allowed to react for 2 hours before EPO-Trac tracer labeled with iodine-125 is added. Following an overnight incubation, the donkey anti-goat precipitating complex (DAG-PPT) secondary antibody is added to the specific assay test tubes (TABLE 1). The DAG-PPT is a donkey anti-goat serum that is pre-precipitated with a normal goat serum and a surfactant. The DAG-PPT is incubated with standards or samples, primary antibody and tracer, for thirty minutes before the test tubes are centrifuged to separate the bound from the unbound tracer. The unbound tracer is removed by decanting the supernatant from each test tube. The bound tracer in the remaining DAG-PPT complex pellets is counted in a gamma counter for 1 minute. The ¹²⁵I counts are inversely proportional to the amount of EPO present in each sample.

Method Comparison:

The IMMULITE EPO procedure was compared to a radioimmunoassay (INCSTAR) on 130 endogenous serum samples, with EPO concentrations ranging from 2.5 to 200 mU/mL. Linear regression analysis yielded the following statistics:

$$(\text{IMMULITE}) = 0.846 (\text{INCSTAR}) + 3.818 \text{ mU/mL} \quad r = 0.978$$

Means: 40.96 mU/mL (IMMULITE)

43.90 mU/mL (INCSTAR)

Conclusion:

The data presented in this summary of safety and effectiveness is the data that the Food and Drug Administration used in granting DPC substantial equivalence for IMMULITE[®] EPO.



**Edward M. Levine, Ph.D.
Director of Clinical Affairs**



Date



DEPARTMENT OF HEALTH & HUMAN SERVICES

JUL 12 1999

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Edward M. Levine, Ph.D.
Director of Clinical Affairs
Diagnostic Products Corporation
5700 West 96th Street
Los Angeles, California 90045-5597

Re: K983203
Trade Name: DPC's IMMULITE® EPO Test Kit
Regulatory Class: III
Product Code: GGT
Dated: March 19, 1999
Received: March 22, 1999

Dear Dr. Levine:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we 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). 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 either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

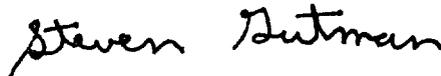
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Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770) 488-7655.

This letter will allow you to begin marketing your device as described in your 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 Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification"(21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597, or at its internet address "<http://www.fda.gov/cdrh/dsma/dsmamain.html>".

Sincerely yours,

A handwritten signature in black ink that reads "Steven Gutman". The signature is written in a cursive style with a large initial 'S' and 'G'.

Steven I. Gutman, M.D, M.B.A.
Director
Division of Clinical
Laboratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

510(k) Number (if known):

K983203

Device Name: IMMULITE® EPO

Indications For Use:

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Concurrence of CDRH, Office of Device Evaluation (ODE)

Patricia Maffei

(Division Sign-Off)

Division of Clinical Laboratory Devices

510(k) Number

K983203

Prescription Use
(Per 21 CFR 801.109)

OR

Over-The-Counter Use