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K992571

i-STAT
CORPORATION

510(k) Summary

This summary of the 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1900 and CFR 807.92.

The assigned 510(k) number is:

Summary prepared on: July 25, 1999

Submitted by:
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Contact:
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Vice President, Regulatory Affairs and Quality Assurance

Establishment Registration Number: 2234478

Identification of Device:

Device Name: Activated Clotting Time Test
Proprietary/Trade Name: i-STAT ® Celite® ACT
Common Name: ACT
Classification: Activated Clotting Time Tests
Device Classification: II
Regulation Number: CFR § 864.7140
Panel: Hematology
Product Code: JBP

Identification of the Predicate Device:

Device Name: Hemochron® Systems Activated Clotting Time

Intended Use of the Device:
The i-STAT Celite Activated Clotting Time (ACT) test cartridge is an *in vitro* diagnostic test used to monitor moderate- and high-level heparin therapy through analysis of arterial and venous whole blood samples. The cartridge is to be used with the i-STAT System 200 model analyzer.

As part of the i-STAT System, the Celite ACT test cartridge is to be used by trained and certified health care professionals in accordance with a facility's policies and procedures.

Description of the Device:
The i-STAT Celite ACT test is contained in a single test cartridge. In use, approximately 40 microliters of fresh whole blood are placed in the cartridge as described below. The cartridge is inserted into the thermally controlled i-STAT Model 200 Portable Clinical Analyzer and all analytical steps are performed automatically. Patient and user information may be entered into the analyzer via a keypad during the automated analysis cycle.

In the i-STAT ACT test the endpoint is indicated by the appearance of an electroactive marker generated by the thrombin-mediated conversion of a synthetic substrate included in the reagent. Detection of the marker indicates generation of thrombin and therefore complete activation of the coagulation cascade. The reported result is calculated from the time and rate of the substrate conversion and is given in seconds. The

reported result correlates to the result of a traditional ACT in which the endpoint is indicated by physical clot formation.

The ACT cartridge is assembled from plastic components that provide the conduits for fluid handling and house the sensor chips. The coagulation test is identified to the user through the name and color code on the cartridge label and by the analyzer through features integral to the cartridge.

In the ACT cartridge the sensor comprises a gold film patterned on a silicon/silicon dioxide substrate.

During the test the blood sample is mixed with reagents which are coated on the cartridge cover in a segment of the sensor channel. The reagent layer includes an activating agent, a thrombin substrate, and inert matrix components. These reagents allow activation of the coagulation cascade and detection of clot formation.

Whole blood is introduced into the sample well of the cartridge at the sample port and the cartridge is closed and inserted into the analyzer. Insertion of the cartridge initiates a controlled and monitored sequence of steps in the instrument. These are:

- Electrical contact is made between the analyzer electronic input circuits and the cartridge. The analyzer identifies the type of cartridge being used and the tests contained in the cartridge.
- The dry chips and sensor channel are heated to 37C.
- The blood is then moved forward. Feedback from the fluid position sensor is used to allow controlled oscillation of the blood segment resulting in dissolution of the reagent layer.
- Following mixing, a count up time is displayed.
- During the course of testing, the position of the blood segment is actively controlled to maintain the length of the blood containing the reagent coincident with the endpoint detector.
- Calculation of sample clot time is performed and displayed.

Comparison to Technological Features of the Predicate Device:
The following technological differences between the i-STAT and the Hemochron Systems Activated Clotting Time tests are noteworthy.

- Endpoint detection in both the Hemochron and i-STAT Systems relies upon detecting the action of thrombin, the final enzyme activated in the coagulation cascade, on a substrate within the sample. In the case of the Hemochron, thrombin converts its natural substrate, fibrinogen, to fibrin which then crosslinks and causes localized or extended clotting throughout the sample. The instrument detects clot formation as the resulting impedance of the magnet's motion through the sample. In the i-STAT test the generated thrombin converts an added substrate to a species which can be detected electrochemically. The signal for the appearance of this marker is used to assign the endpoint time. Because the traditional ACT test is not highly sensitive to fibrinogen, however, this does not cause a method-to-method bias that is a function of the fibrinogen level for fibrinogen values greater than 100 mg/dl. Below 100 mg/dl the Hemochron result may be prolonged relative to that of the i-STAT.

- The volume of blood required for the Hemochron and i-STAT tests is significantly different. The Hemochron requires either 2.0 or 0.4 ml of blood depending on the tube type where the i-STAT test requires 0.040 ml. Although such a difference does not necessarily imply systematic differences in the results of test methods, in this case it is a contributor to a between method bias that is a function of the pre-analytical temperature of the blood. The relatively long time constant for sample heating in the Hemochron results in prolongation of results with hypothermic samples.

Summary of Non-Clinical Performance in Support of Substantial Equivalence:

- Studies using ex-vivo heparinized whole blood samples establish that the i-STAT Celite ACT test responds linearly to the heparin concentration across its reportable range of 50 to 1000 seconds. The

average sensitivity across multiple donors is 77 seconds / U/ml heparin. This is equivalent to the sensitivity of the Hemochron System Activated Celite Clotting Time test.

- From the heparin linearity experiments it can be seen that the within-sample reproducibility of the i-STAT test is 5.6% in samples spanning the reportable range. The Hemochron Celite ACT package insert indicates imprecision of 8.8% in whole blood samples
- The imprecision of the i-STAT test in plasma controls was established using in-house and user studies. Overall the Level 1 and Level 2 Controls read 221 ± 19 seconds (8.4% C.V.) and 456 ± 22 seconds (4.8% C.V.), respectively. This includes within-lot, lot-to-lot, vial-to-vial, analyzer-to-analyzer, and operator-to-operator components of the imprecision. The total imprecision in whole blood controls reported for the Hemochron Celite ACT is 6.5% and 5.3% for Level 1 and Level 2 Controls, respectively.

Summary of Clinical Test Performance in Support of Substantial Equivalence Claims:
Studies conducted at three external sites compared the results of the i-STAT Celite ACT (y) to those of the predicate device (x) for samples from cardiac catheterization and bypass procedures. The identical sample was tested on each instrument. The methods were compared using least square regression analysis. The results are summarized in the table below.

Statistic	Definition	Site 1	Site 2	Site 3
N	The number of patient samples used in the comparison	118	74	101
Mean	The average of the comparative method result over the sample population	272	396	371
Range	The range of comparative method results obtained over the sample population	887	1182	1079
S_x	The standard deviation of the comparative method results across the sample population	180	240	272
Slope	The least squares linear regression estimate of the slope	1.00	0.951	0.902
Intercept	The least squares linear regression estimate of the intercept	0	25	24
Correlation	The correlation coefficient calculated from linear regression	0.949	0.923	0.949
s_{yx}	The standard error of the estimate of the regression of y on x	94	97	55
s_{yx}%	The relative standard error of the estimate	15.9%	15.7%	12.6%
s_{xx}%	Relative within-sample imprecision of the comparative method over the sample population	9.1%	9.7%	6.7%
s_{yy}%	Relative within-sample imprecision of the test method over the sample population	5.6%	4.4%	4.7%

A comparison of the i-STAT and comparative method was also performed at two sites using samples from patients undergoing hemodialysis and extra-corporeal membrane oxygenation. Because the limited range of the results precludes comparison using linear regression, the average bias of the methods was determined. The results are presented in the table below.

Parameter	Definition	Site 1	Site 2
Number	Number of patient samples used in the comparison	52	14
Mean	The average of the comparative method result over the sample population	189	213
Range	The range of comparative method results obtained over the sample population	93-270	199-233
Mean bias	Average bias between the i-STAT and comparative method	-24	-24
s_x	Standard deviation of the comparative method results across the sample population	37	10
s_{xx}	Pooled imprecision of the x duplicates	16	10
s_{yy}	Pooled imprecision of the y duplicates	9	6
s_{yx}	The standard error of the estimate of the regression of y on x	19	8

Limitations:
The i-STAT Celite ACT test is to be used with fresh venous or arterial whole blood samples. The presence of exogenously added heparin, citrate, oxalate, or EDTA will interfere with test results. Poor technique in sample collection may also compromise the results. Samples drawn from insufficiently flushed catheters or from traumatic venipunctures may be contaminated with interfering substances. Samples should be collected into plastic syringes or tubes. Collection into glass may prematurely activate coagulation resulting in accelerated clotting times.

The i-STAT ACT test uses Celite brand diatomaceous earth as the activator of the intrinsic pathway. The result may, therefore, be prolonged in the presence of aprotinin. **The test is not recommended for use with patients receiving aprotinin.**

Hemodilution, platelet dysfunction, factor deficiencies, and dysprothrombinemias may affect the results of this test.

The i-STAT ACT test is not affected by hematocrit in the range of 20 - 70%, fibrinogen concentration in the range from 100 - 500 mg/dL, or sample temperature from 15 - 37ºC.

Conclusions:
Based on the non-clinical data the i-STAT Celite ACT test responds linearly to heparin concentration in the range from 50-1000 seconds, is insensitive to sample temperature, hematocrit, and fibrinogen. Studies using plasma controls and whole blood indicate adequate precision for normal and prolonged clot times. Clinical data indicates acceptable correlation to the predicate device.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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FEB 1 0 2000

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Quality Assurance
i-STAT Corporation
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Re: K992571
Trade Name: i-STAT® Celite® ACT
Regulatory Class: II
Product Code: JBP
Dated: December 21, 1999
Received: December 22, 1999

Dear Dr. VanDerWerf:

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.

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" (21CFR 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,

Steven Gutman

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

3 Indications for use

510(k) Number (if known): K992571

Device Name: **Celite ACT test.**

The i-STAT Celite ACT test is useful for monitoring patients receiving heparin for treatment of pulmonary embolism or venous thrombosis, and for monitoring anticoagulation therapy in patients undergoing medical procedures such as catheterization, cardiac surgery, surgery, organ transplant and dialysis.

Peter E. Maheux

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K992571

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Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓ OR Over-The-Counter-Use _____

(Per 21 CFR 801.109) (Optional Format 1-2-96)