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APPROVAL ORDER

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OOM-1354



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAY 11 2000

Ms. Tammy Carrea
Quality Affairs Manager, Product Development
Cardiovascular Diagnostics, Inc.
5301 Departure Drive
Raleigh, North Carolina 27616

Re: H990012
TAS Ecarin Clotting Time Test
Filed: November 8, 1999
Amended: November 23, 1999 and May 3, 2000

Dear Ms. Carrea:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for the TAS Ecarin Clotting Time Test. This device is indicated to be used to determine the anticoagulant effect of recombinant hirudin (r-hirudin) during cardiopulmonary bypass in patients who have heparin induced thrombocytopenia (HIT). CDRH is pleased to inform you that your HDE is approved subject to the enclosed "Conditions of Approval." You may begin commercial distribution of the device after you have submitted an amendment to this HDE with copies of the approved labeling in final printed form.

The sale, distribution, and use of this device are limited to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)). In addition, in order to ensure the safe use of the device, FDA has further restricted the device within the meaning of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act (21 U.S.C. 352(q) and (r)).

FDA wishes to remind you that failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

CDRH will notify the public of its decision to approve your HDE by making available a summary of the safety and probable benefit of the device upon which the approval was based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/cdrh/ode/hdeinfo.html>. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers

Page 2 – Ms. Tammy Carrea

Lane, Rm. 1061, Rockville, MD 20852. The written request should include the HDE number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

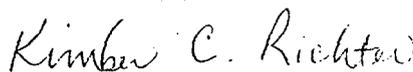
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this HDE submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when HDE applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at <http://www.fda.gov/cdrh/pmat/pilotpmat.htm> for further details.

Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Peter E. Maxim, Ph.D. at (301) 594-1293.

Sincerely yours,



Kimber C. Richter, M.D.
Deputy Director for Clinical
and Review Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

CONDITIONS OF APPROVAL FOR AN HDE

I. APPROVED LABELING

As soon as possible and before commercial distribution of the device, the holder of an HDE should submit three copies of the approved labeling in final printed form as an amendment to the HDE. The supplement should be submitted to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

II. ADVERTISEMENTS

Advertisements and other descriptive printed materials issued by the HDE holder or private label distributor with respect to this device should not recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)), all advertisements and other descriptive printed material issued by the holder or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

III. HDE SUPPLEMENTS

Before making any change affecting the safety or probable benefit of the device, the HDE holder should submit a supplement for review and approval by FDA unless a "Special HDE Supplement" is permitted as described under 21 CFR 814.39(d)(2) or an alternate submission is permitted as described under 21 CFR 814.39(e). All HDE supplements or alternate submissions must comply with the applicable requirements under 21 CFR 814.39 of the Premarket Approval (PMA) regulation and under 21 CFR 814.108 of the Humanitarian Device Exemption regulation. The review timeframe for HDE supplements is 75 days except for those submitted under 21 CFR 814.39(e).

Since all situations which require an HDE supplement cannot be briefly summarized, please consult the HDE regulation for further guidance. The guidance provided below is only for several key instances. In general, an HDE supplement must be submitted:

- 1) When unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification; or
- 2) If the device is to be modified, and animal/laboratory or clinical testing is needed to determine if the modified device remains safe and continues to provide probable benefit.

HDE supplements submitted under 21 CFR 814.39(d)(2) "Special HDE Supplement - Changes Being Effected" are limited to the labeling, quality control, and manufacturing process changes as specified under this section of the regulation. This provision allows for the addition of, but

not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented upon acknowledgment by FDA that the submission is being processed as a "Special HDE Supplement - Changes Being Effected." Please note that this acknowledgment is in addition to that issued by the Document Mail Center for all HDE supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software, or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of an HDE supplement before implementation and include the use of a *30-day HDE supplement* or *periodic postapproval report*. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence to the HDE holder that the alternate submission is permitted for the change. Before this can occur, FDA and the HDE holder must agree upon any needed testing, the testing protocol, the test results, the reporting format, the information to be reported, and the alternate submission to be used.

Please note that unlike the PMA process, a supplement may not be submitted for a new indication for use for a humanitarian use device (HUD). An HDE holder seeking a new indication for use for an HUD approved under the provisions of Subpart H of 21 CFR 814, must obtain a new designation of HUD status for the new indication for use and submit an original HDE application in accordance with §814.104. The application for the new indication for use may incorporate by reference any information or data previously submitted to the agency.

IV. POSTAPPROVAL RECORD KEEPING REQUIREMENTS

An HDE holder is required to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing institutional review boards (IRBs), as well as any other information requested by a reviewing IRB or FDA.

V. POSTAPPROVAL REPORTING REQUIREMENTS Continued approval of the HDE is contingent upon the submission of postapproval reports required under 21 CFR 814.84 and 21 CFR 814.126.

A. ANNUAL REPORT

Annual reports should be submitted at intervals of 1 year from the date of approval of the original HDE. Reports for supplements approved under the original HDE should be included in the next and subsequent periodic reports for the original HDE unless otherwise specified in the approval order for the HDE supplement. Three copies identified as "Annual Report" and bearing the applicable HDE reference number are to be submitted to the HDE Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Reports should indicate the beginning and ending date of the period covered by the report and include the following information required by 21 CFR 814.126(b)(1):

1. An update of the information required under §814.102(a) in a separately bound volume;
2. An update of the information required under §814.104(b)(2), (b)(3), and (b)(5);
3. The number of devices that have been shipped or sold and, if the number shipped or sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;
4. Information describing the applicant's clinical experience with the device. This shall include safety information that is known or reasonably should be known to the applicant, a summary of medical device reports made pursuant to 21 CFR 803, any data generated from postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device labeling; and
5. A summary of any changes made to the device in accordance with supplements submitted under §814.108 and any changes required to be reported to FDA under §814.39(b).

B. ADVERSE REACTION AND DEVICE DEFECT REPORTING

As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and probable benefit of the device, the holder shall submit three copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Such reports should be submitted within 10 days after the HDE holder receives or has knowledge of information concerning:

- (1) A mixup of the device or its labeling with another article.
- (2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and
 - (a) has not been addressed by the device's labeling or
 - (b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

- (3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved HDE that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the HDE holder's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the firm. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the holder shall be included in the "Annual Report" described under "Postapproval Reports" above unless otherwise specified in the conditions of approval for this HDE. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of occurrence for each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the HDE holder when determined by FDA to be necessary to provide continued reasonable assurance of the safety and probable benefit of the device for its intended use.

C. REPORTING UNDER THE MEDICAL DEVICE REPORTING REGULATION

The Medical Device Reporting regulation (MDR) (21 CFR 803) became effective on April 11, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices:

- (1) may have caused or contributed to a death or serious injury; or
- (2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Events subject to reporting under the MDR regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements. FDA has determined, however, that such duplicative reporting is unnecessary. Therefore, whenever an event involving a device is subject to reporting under both the MDR regulation and the "Adverse Reaction and Device Defect Reporting" requirements, the report should be submitted in compliance with Part 803 and identified with the HDE reference number to Food and Drug Administration, Center for Devices and Radiological Health, Medical Device Reporting, PO Box 3002, Rockville, Maryland 20847-3002. For questions regarding the MDR regulation, please call (301) 594-2735.

Events included in periodic reports to the HDE that have also been reported under the MDR regulation must be so identified in the periodic report to the HDE to prevent duplicative entry into FDA information systems.

Copies of the MDR regulation and FDA publications, entitled "An Overview of the Medical

Device Reporting Regulation" and "Medical Device Reporting for Manufacturers," are available on the CDRH WWW Home Page (<http://www.fda.gov/cdrh>), through CDRH's Fact-on-Demand (FOD) at 800-899-0381 (FOD # 336, 1336, 509 and 987) or by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Lane
Rockville, Maryland 20850

SUMMARY OF SAFETY AND
PROBABLE BENEFIT

SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. General Information

Device generic name: Ecarin Clotting Time Test

Device trade name: Thrombolytic Assessment System (TAS™)
Ecarin Clotting Time (ECT™), hereinafter
referred to as TAS ECT

Applicant's Name and Address: Cardiovascular Diagnostics, Inc.
5301 Departure Drive
Raleigh, NC 27616

HDE number: H990012

Date of Humanitarian Use Device (HUD) Designation: September 23, 1999

Date of Panel Recommendation: Not applicable. (See Section XII for discussion).

Date of Good Manufacturing Practices inspection: January 15, 1998

Date of notice of approval to the applicant: MAY 11 2000

II. Indications for Use

The TAS ECT Test Card is to be used with the TAS Analyzer and is intended to be used to determine the anticoagulant effect of recombinant hirudin (r-hirudin) during cardiopulmonary bypass in patients who have heparin-induced thrombocytopenia (HIT).

III. Device Description

The TAS ECT is to be used with the TAS Analyzer (K990566) to monitor beyond the therapeutic levels (0-3 µg/mL) of r-hirudin to the higher levels (3-5 µg/mL) required during cardiopulmonary bypass (CPB) in citrated whole blood. The test is for *in vitro* diagnostic use, and is specifically intended for professional use during CPB procedures.

A. TAS ECT Test Card

A TAS ECT Test Card is composed of a thin plastic card the size of a standard credit card, upon which is mounted a flat, shallow reaction chamber. The chamber is formed by a spacer, which determines the reaction volume, and an optically transparent cover piece. A sample well is connected to the reaction chamber by a conduit. The reaction chamber contains all the reagents

necessary for a particular test. The reagents are dry, which infers maximum stability. Also contained in the reaction chamber are paramagnetic iron oxide particles (PIOP), which move under the influence of magnetic fields in the instrument. When the sample drop is added to the reaction chamber, the mix of particles and reagents is reconstituted. On the back of the test card is a magnetically encoded stripe containing lot-specific information such as test type, lot number, expiration date, allowed sample types, and mathematical parameters specific for the lot. This information is read by the TAS Analyzer upon initiation of a test.

B. TAS Analyzer

The TAS Analyzer produces an oscillating magnetic field using an electromagnet with an alternating field and a thin permanent magnet mounted at a right angle above it. An inserted test card lies just above this assembly, which also contains a heater strip to maintain a set point temperature (37°C). The reaction chamber is illuminated with a light emitting diode mounted adjacent to the photodiode, and light reflected from the test card surface is measured. The photodetector in the instrument "sees" a light change when the sample is added and begins the test. The electromagnet turns off and on every second. The particles stand up when the magnet is on, causing more light to pass through the detector, and fall down when it is off, causing less light to be detected. This movement of the particles produces the alternating current (AC) signal.

The signal response emerges as a double-sided waveform, with the higher amplitude side detected when the electromagnet is on and the lower amplitude side when the magnet is off. This double-sided waveform is subsequently filtered to yield a single sided waveform, which shows maximum amplitude when the PIOP movement is greatest. Formation of a clot in the sample impedes PIOP movement. The signal produced by the relative movement of the PIOP is interpreted by the analyzer in accordance with algorithms predetermined for this purpose and clotting times are reported in seconds.

C. TAS ECT Test

The TAS ECT Test provides a one stage, two step test which measures the clotting time of a sample after combining it with the prothrombin activator, ecarin. This test consists of a single card that contains calcium chloride and the enzyme, ecarin, which catalyzes the hydrolytic cleavage of the 323Arg-324Ile bond in the human prothrombin molecule, whereby thrombin activity is generated without the release of any zymogen fragment. This form of active prothrombin has been termed "meizothrombin" and is inhibited by r-hirudin, but not efficiently by the heparin-ATIII complex.

The TAS ECT Test Card is to be used with the TAS Analyzer and is intended to determine the anticoagulant effect of recombinant hirudin in plasma diluted, citrated whole blood. Samples are obtained by drawing whole blood into sodium citrate (3.2 or 3.8%), in a ratio of nine parts blood to one part anticoagulant, and by mixing briefly with gentle inversion. The sodium citrate chelates the calcium in the blood. This allows the operator to control the start of the clotting reaction. The test card has a magnetic stripe on the back, which encodes lot specific information such as lot number, expiration date, and mathematical parameters specific to that lot. A room temperature test card is removed from the pouch and the card is passed through the TAS instrument's magnetic reader to initiate the instrument to run a TAS ECT test. The instrument instructs the operator to insert a TAS ECT test card and then requests patient and sample information. The card is warmed quickly and the operator is prompted to add a drop of sample to the card well. The sample is drawn into the card and rehydrates the TAS ECT reagent, which begins the clotting reaction. As the reaction proceeds and clotting begins, the movement of the particles decreases, and the instrument signals the clotting time.

The greater the amount of an antithrombin drug in the patient, the more meizothrombin (generated by the action of ecarin on prothrombin in the sample) is inhibited and the longer the clotting time reported by the TAS system.

IV. Contraindications

The use of the TAS ECT test is contraindicated in the following individuals:

- Patients on coumadin therapy with an INR > 4.5,
- Patients with > 25 percent hemolysis,
- Patients with > 30 percent hemodilution,
- Patients with > 0.5 U/mL, concentration of unfractionated heparin,
- Patients with < 30 percent prothrombin activity or < 15 mg/dL fibrinogen concentration, and
- Patients on thrombolytic therapy.

The use of acid citrate blood collection tubes is also contraindicated with the TAS ECT.

V. Warnings and Precautions

See "Warnings and Precautions" in the labeling.

VI. Alternative Practices and Procedures

The process of cardiopulmonary bypass (CPB) causes significant hemodilution and the potential activation of the coagulation cascade with unpredictable and occasionally progressive consumption of several coagulation factors. Usually

high dose heparin is used to anticoagulate during CPB, but it is contraindicated and life-threatening in patients experiencing heparin-induced thrombocytopenia (HIT). Refludan (r-hirudin) has been found to be a reasonable substitute for heparin in HIT.

While there exists alternative in vitro diagnostic procedures (IVDs), including global coagulation tests, such as the activated clotting time (ACT), activated partial thromboplastin time (aPTT), or prothrombin time (PT), performance has not been established for monitoring high dose r-hirudin (3-5 µg/mL) in blood during CPB. Non-controlled studies using global coagulation tests, such as the aPTT and the ACT, for r-hirudin monitoring during CPB have yielded variable results because the coagulation factors necessary for the aPTT and ACT may be depleted or absent. Additionally, potential matrix effects (hemodilution, consumption of coagulation factors), lack of standardization, and an apparent non-linear, dose-response of aPTT to higher concentrations (>1.5 µg/mL) of r-hirudin (Tripodi et. al., 1993) also contribute to variable results.

VII. Marketing History

The TAS ECT test has been provided to two consultants in Germany for Investigational Use Only. A limited number of clinical uses (10), performed under Compassionate Use, have been recently done in the United States.

VIII. Potential Adverse Effects of the Device on Health

Inaccurate information on the coagulation status of the patient poses a significant risk to the patient during CPB, since both over-treatment and under-treatment can have fatal consequences (bleeding in the patient and clots in the CPB system, respectively). Possible risks of using the TAS ECT Test Card could include under-estimation or over-estimation of the level of hirudin in the patient. Currently, an antidote for hirudin is unavailable, and the clinical data available are insufficient to establish the probabilities or incidence of erroneous medical judgements and their clinical outcomes.

IX. Summary of Preclinical Studies

A. Precision Studies.

Precision studies were performed on the TAS Analyzer with TAS ECT cards and the indicated sample types. Test cards and samples were allowed to reach room temperature before testing. Unless otherwise stated, thirty replicates of each sample type were tested, to allow coefficients of variation to be determined at a 95% confidence level.

1. Within day

In this study, one operator performed all of the tests on a single day, using a single lot of TAS ECT cards. The test was done with two sample types: citrated whole blood (CWB) and CWB with 4.0 ug/mL r-Hirudin, individually diluted at 30% with phosphate-buffered saline (PBS). All samples were diluted 1:1 with normal human plasma before addition to the TAS ECT test. Testing was done on 30 TAS Analyzers simultaneously, to minimize changes in the samples that might occur during the course of the experiment, therefore the results of this test also include analyzer variation.

	Mean (seconds)	Standard Deviation (seconds)	%CV
r-Hirudin Concentration			
0.0 ug/mL	55.1	2.8	5.0
4.0 ug/mL	443.4	27.4	6.2

2. Day to day

Day to day precision studies of 10 TAS ECT cards were done each day, for 20 consecutive days. Single lots of TAS ECT normal and abnormal control plasma and of TAS ECT cards were used in the study. A single operator did the tests on multiple TAS Analyzers. These data were analyzed according to Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline, NCCLS publication EP5-A, Volume 19 Number 2.

	Normal Control (seconds)		Abnormal Control (seconds)			
	Range		Range			
	Min.	Max.	Min.	Max.		
Mean	52.9	50.8	54.7	154.0	146.1	159.9
Total Precision (SD)	2.2			9.2		
Total CV	4.1			6.0		

Day to day precision studies were also done on CWB samples, neat and CWB containing 4.0 ug/mL r-hirudin. Results are in Table 2a.

Table 2a: Day to Day Variation of ECT Test Card (CWB)						
Day to Day Variation of ECT Test Card: Citrated Whole Blood (CWB)						
(N=5 samples per day for 20 days)						
CWB with 0.0 µg/ml r-hirudin				CWB with 4.0 µg/ml r-hirudin		
Range				Range		
		Min	Max		Min	Max
Mean (seconds)	55.9	49.0	60.6	439.4	393.0	529
Total Precision (S.D.)	4.1			35.5		
Total CV (%)	7.0			6.7		

3. Operator to operator variability

Three different operators performed all of the tests on a single day, on 45 TAS Analyzers, with a single lot of TAS ECT cards. The test was done with two sample types, diluted at 30% with PBS: citrated whole blood and citrated whole blood with 4.0 ug/mL r-hirudin. To minimize variation that might occur due to sample changes with time, the tests were performed with 15 analyzers/operator, by 3 operators simultaneously.

Table 3: Operator to Operator Precision Results Individually Diluted Samples						
	Mean (seconds)	Standard Deviation (seconds)	% CV	Grand Mean (seconds)	Grand SD	Grand CV
Results for 0.0 ug/mL r-Hirudin						
Operator I	49.8	3.1	6.2			
Operator II	50.7	2.7	5.3	50.9	2.9	5.8
Operator III	52.2	2.6	5.0			
Results for 4.0 ug/mL r-Hirudin						
Operator I	405.3	30.1	7.4			
Operator II	396.0	22.8	5.8	406.8	27.0	6.6
Operator III	419.2	23.1	5.5			

4. Lot to lot

Lot to lot precision studies were performed with TAS ECT tests using r-hirudin at 0.0 and 2.0 ug/mL, in citrated whole blood, with 40 replicate values. A single operator did the tests on multiple TAS Analyzers. This experiment was performed without the 1:1 pooled normal plasma dilution, to test the relative response of the different lots of TAS ECT tests and lot variation that would occur from the 1:1 plasma dilution.

Lot #	r-hirudin	Mean (seconds)	SD (seconds)	% CV
1	0.0	48.6	2.4	5.0
	2.0	428.6	19.9	4.7
2	0.0	49.3	2.0	4.1
	2.0	397.6	27.8	7.0
3	0.0	48.6	2.0	4.0
	2.0	434.1	25.2	5.8

B. Normal Range and Expected Values.

Samples from 120 normal individuals (72 females and 48 males ranging in age from 20 to 63 years, median 38 years) were tested using the TAS Analyzer and TAS ECT Test Cards. Citrated whole blood was diluted 1:1 with pooled normal human plasma. The results are presented in Tables 5-7.

	REP 1	REP 2	Mean
	Seconds		
Geomean	48.5	48.3	48.5
Mean	48.7	48.5	48.6
STDEV	3.8	4.0	3.4
%CV	7.7	8.3	7.1
Minimum	32.5	29.3	30.9
Maximum	58.8	57.1	54.9
Number	120	120	120

	Age	N=	REP 1	REP 2	Mean
			Seconds		
Median Age = 38	< 38	63	48.9	48.5	48.7
	> 38	57	48.4	48.5	48.5
T-test			0.526	0.955	0.706

	Normal TAS-ECT (seconds)
Mean	48.5
STDEV	3.4
% CV	7.1
Minimum	30.9
Maximum	54.9

C. Interfering Factors.

Several studies were performed to determine whether certain factors could interfere with the TAS-ECT test. The results are summarized in Table 8.

Table 8: Interfering Factors

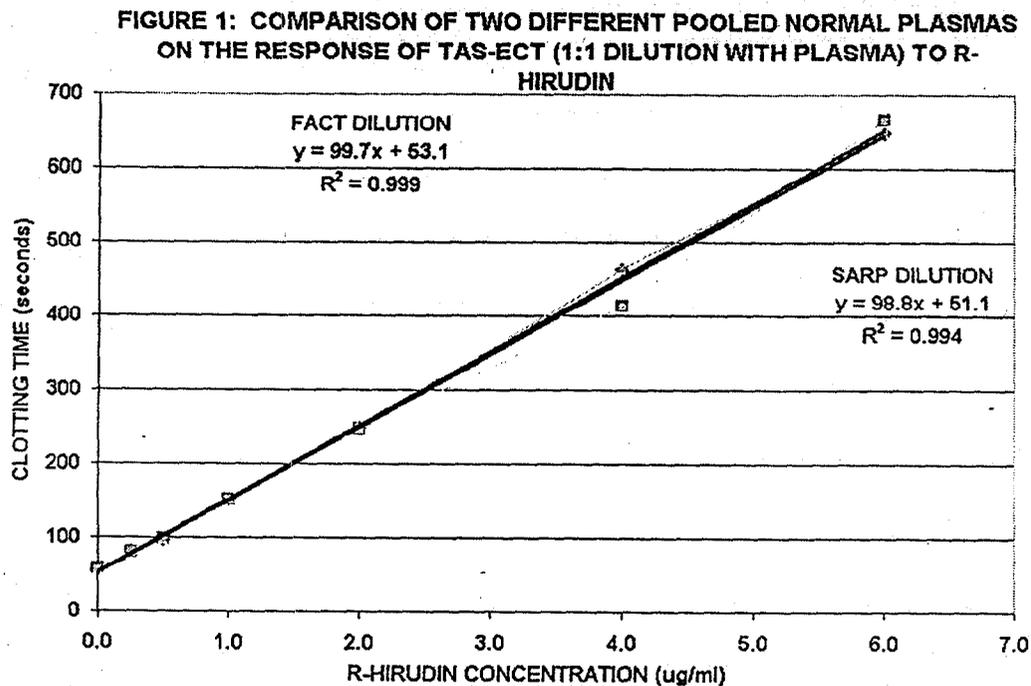
Factor Sensitivity
Factor VII tested 0 to 100 % normal - No effect on TAS ECT Test performance
Factor IX tested 0 to 100 % normal - No effect on TAS ECT Test performance
Factor X tested 0 to 100 % normal - No effect on TAS ECT Test performance
Factor II tested 0 to 100 % normal - No effect on TAS ECT Test performance > 30% normal
Fibrinogen tested at 15 to 1000 mg/dl - No effect on TAS ECT Test performance
Interference Studies
Acid Citrate blood collection tubes - contraindicated
Hematocrit tested at HCT of 8 to 64% - no effect on TAS ECT Test performance
Heparin tested at 0.0, 0.5, and 5.0 U/mL - No effect up to 0.5 U/mL unfractionated heparin on TAS ECT Test performance
Lipemia tested at 0.0 to 15.0 g/l - No effect on TAS ECT Test performance
Nitroglycerin tested at 0 to 1000 ug/mL - No significant effect on TAS ECT Test performance
Dextran tested at 0 to 5 mg/mL - No significant effect on TAS ECT Test performance
Plasminogen tested at 0 to 100 % normal - No effect on TAS ECT Test performance >20% normal
Protamine tested at 0 to 100 ug/mL - No effect on TAS ECT Test performance
Hemodilution tested at 0 to 100% No significant effect on TAS ECT Test performance at <30% hemodilution
Aprotinin test at 0.0 to 1000 KIU/mL - No effect on TAS ECT Test performance
Citrate at 3.2% vs. 3.8% has no effect
Hemolysis of Sample tested at 0 to 100 % hemolysis; up to 25% hemolysis no effect

In addition, studies demonstrated that there was no interference on the assay when:

- Sample temperature was 4°C, 24°C, or 37°C;
- Test cards were 4°C or ambient temperature;
- Samples were stored in glass or polypropylene tubes.

D. Dilution with normal human plasma.

Fresh citrated whole blood was diluted at 30% with phosphate buffered saline (PBS). The PBS/blood mixture was supplemented with various concentrations of r-hirudin and the aliquots were diluted 1:1 with either FACT or SARP plasma, and 5 replicate measurements were performed on TAS ECT tests (30 μ l/test). Results are shown in the graph below. Both FACT and SARP normal pooled plasmas yielded equivalent sensitivity to r-hirudin.



FACT – (F)actor (A)ssay (C)on(T)rol

SARP – (S)pecialty (A)ssayed (R)eference (P)lasma

E. Analytical Sensitivity of TAS ECT Test.

The lowest level of hirudin that could be detected in plasma was 0.1 μ g/mL.

F. Stability Studies.

Studies conducted support a stability of 24 months for the unopened test cards when stored at 2-8°C.

X. Summary of Clinical Studies

The TAS ECT Test was used, when requested, on a compassionate use basis, in

10 patients at 9 geographically diverse clinical sites. Six males and three females were identified and ranged in ages from 14-82 years. Age was not provided for one male patient, and no patient information was provided for another. In cases where r-hirudin dosing information was provided, the 1:1 plasma diluted ECT test responded to increases in dosing. The diluted ECT, during the cardiac procedures, was generally maintained between 200-450 seconds.

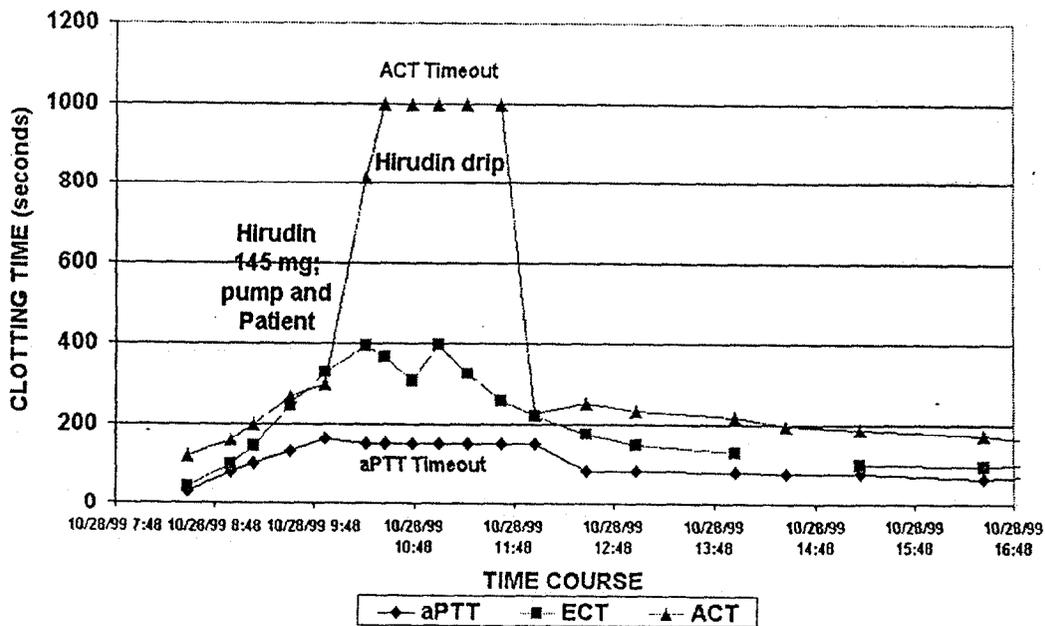
Summary of patient data

The patient population included persons identified with and/or confirmed as a high risk for HIT, and requiring high dose anticoagulation with recombinant hirudin for a scheduled or emergency CPB procedure.

The patients were treated and monitored for their responses to the drug, r-hirudin. The device was used according to procedures outlined in the package insert, with sites taking readings at baseline, during bolus and/or pump dosing and/or titers. Response to the drug was evident in all 10 patients.

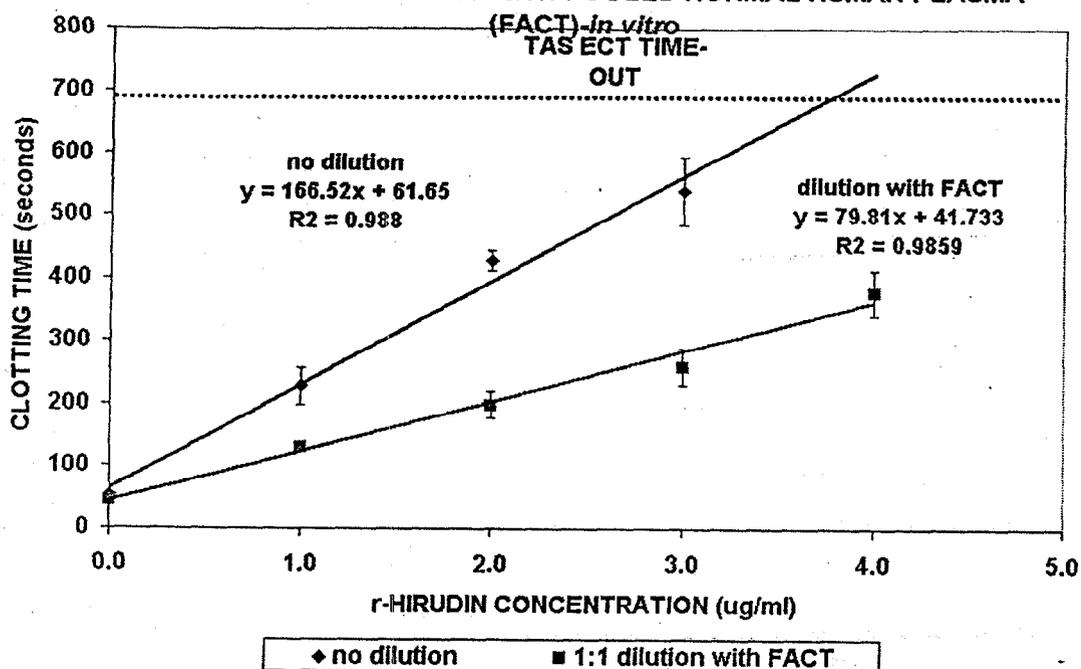
In one subset of four patients, a comparative analysis with the aPTT and ACT provided results which indicated that neither test was sufficiently sensitive nor linear to monitor r-hirudin at the higher doses used during CPB (See the example in Figure 2).

FIGURE 2: COMPARISON OF TYPICAL TAS ECT, APTT, AND ACT RESPONSE TO r-HIRUDIN BOLUS AND INFUSION DURING CPB SURGERY



In another subset, three patients demonstrated that an undiluted ECT exceeds the linear range for monitoring the drug at those higher levels (See the example in Figure 3).

FIGURE 3: TAS ECT RESPONSE TO r-HIRUDIN IN WHOLE CITRATED BLOOD AND DILUTED 1:1 WITH POOLED NORMAL HUMAN PLASMA



Although instructions were provided to the sites, and data were requested, each site provided varying levels and complexities of data. During cardiac procedures, the collective ranges of the diluted ECT were between 200 - 450 seconds. Values not exceeding 600 seconds during the testing period, ranged from 141.8 - 485.1 seconds.

In one patient, an episode of bleeding occurred due to an inability to reverse the effects of r-hirudin. Another patient, who was hypercoagulable and presented with compromised renal function, developed significant postoperative coagulopathy; and required multiple units of platelets, packed red cells, cryoprecipitate and fresh frozen plasma. Although postoperative bleeding events occurred in these two patients, they were soon corrected with no further problems.

Safety evaluation: Two patient deaths were reported, the first of which was a 63-year old male. The cause of death was reported as due to "severe myocardial depression and the severity of his disease," and was not attributed to the use of the device for monitoring anticoagulation.

The second patient died post-operatively. This patient was noted to have a severe coagulopathy possibly related to the r-hirudin therapy, possibly attributable to other causes.

The precision and accuracy of the TAS ECT under conditions of actual clinical use are not known. The available data do suggest, however, a general response to the ECT to increasing or decreasing doses of r-hirudin drug.

Two of ten patients whose r-hirudin therapies were monitored with this device experienced profound coagulopathies. The TAS ECT appeared to not be sensitive to the abnormalities of hemostasis observed in these patients.

XI. Conclusions Drawn from the Studies

The TAS ECT test is to be used only for patients who have been identified with and/or confirmed as a high risk for heparin induced thrombocytopenia (HIT) and require high dose anticoagulation with recombinant hirudin for a scheduled or emergency cardiopulmonary bypass (CPB) procedure.

Preclinical studies show that the TAS ECT test provides a method for monitoring high dose (3 – 5 ug/mL) r-hirudin. In the required monitoring range, the test is not significantly affected by most interferences that would be commonly found during CPB. The TAS ECT test results are affected by very low concentrations of prothrombin (< 30% normal), hemolysis > 25% and hemodilution > 30%. These conditions are not likely to be encountered, even during CPB procedures.

The limited clinical data are not adequate to establish the safety and effectiveness of this device in the indicated patient population. The limited clinical reports, of 10 patients, show that the TAS ECT test responds to increasing levels of r-hirudin in the high dose range used for CPB and provides a tool for monitoring r-hirudin during CPB. Limited clinical studies have also shown that neither aPTT nor ACT tests provide a reliable means for monitoring high dose r-hirudin, whereas, during the same procedures, the TAS ECT responded as predicted from the preclinical studies. Clinical data are limited, but indicate satisfactory monitoring of r-hirudin drug levels.

In conclusion, the pre-clinical safety and performance studies provide reasonable assurance that the device materials and design are appropriate for this intended use. The limited clinical data suggest that the device will not expose patients to an unreasonable or significant risk of illness or injury. Considering the risks and benefits of currently available devices or alternative forms of monitoring high-dose r-hirudin in blood during CPB, it appears that the probable benefit to health from using the device outweighs the risk of injury or illness.

XII. Panel Recommendations

The HDE was not reviewed by an FDA Advisory Panel. A similar device, the activated whole blood clotting time test (ACT), for a different indication, was reviewed by the Hematology and Pathology Devices Panel on September 12, 1980. Since that meeting, many similar devices have been cleared by the FDA.

Therefore, it was determined that this application substantially duplicates information previously reviewed by the Advisory Panel.

XIII. CDRH Decision

CDRH has determined that, based on the data submitted in this HDE application, the TAS ECT Test will not expose patients to an unreasonable or significant risk of illness or injury; and that the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval order on

MAY 11 2000.

XIV. Approval Specifications

Directions for Use. See professional labeling (attached).

Contraindications, Precautions and Warnings. See professional labeling.

XV. References (Bibliography)

1. Tripodi A, Chantarangkul V, Arbini AA, Moia M, Mannucci PM. Effects of Hirudin on Activated Partial Thromboplastin Time Determined with Ten Different Reagents. *Thrombosis and Haemostasis*, 70 (2) pp. 286-288, 1993.

LABELING



TAS™ ECT™ Test Card

Kit Containing 25 ECT Test Cards

For *in vitro* diagnostic use only

Humanitarian Device: Authorized by Federal Law for use in determining the anticoagulant effect of recombinant hirudin (r-hirudin) during cardiopulmonary bypass (CPB) in patients who have heparin-induced thrombocytopenia (HIT). The effectiveness of this device for this use has not been demonstrated.

Federal law restricts this device for sale and distribution to, or on the order of, a physician or to a clinical laboratory. Use is restricted to, by, or on the order of a physician.

Intended Use

The TAS™ (Thrombolytic Assessment System) Ecarin Clotting Time (ECT) Test Card is to be used with the TAS Analyzer and is intended to determine the anticoagulant effect of r-hirudin during cardiopulmonary bypass in patients who have heparin-induced thrombocytopenia.

The TAS ECT (the TAS ECT Test Card together with the TAS Analyzer) is suited for professional use in decentralized areas of testing near the site of patient care as well as for use in the more traditional clinical laboratory.

Monitoring with the TAS ECT is indicated for persons who have been identified with and/or confirmed as a high risk for HIT, and require high dose anticoagulation with recombinant hirudin for a scheduled or emergency CPB procedure.

Contraindications

TAS ECT is contraindicated for patients on coumadin therapy with an INR > 4.5, patients with > 25% hemolysis, patients with > 30% hemodilution, patients with > 0.5 U/ml concentration of unfractionated heparin (UFH), and patients with less than 30% prothrombin activity or 15 mg/dl fibrinogen concentration. Patients on thrombolytic therapy should not be monitored with the TAS ECT. The use of acid citrate blood collection tubes is also contraindicated with the TAS ECT.

Summary and Explanation

Ecarin, a protein prothrombin activator from *Echis carinatus* venom (E.C. 3.4.99.27), was isolated by Kornalik et al. in 1969.¹ Ecarin causes coagulation of citrated whole blood (CWB) or citrated plasma (CP) by the calcium-independent activation of prothrombin. Ecarin has been characterized by Morita et al.² and by Kornalik and Blomback³ as a single chain glycoprotein with a molecular weight of 55-60 kDaltons which exerts metalloproteinase activity inhibited by EDTA, glutathione, cysteine, and mercaptoethanol. Common serine proteinase inhibitors such as diisopropyl-fluorophosphate (DFP), soybean trypsin inhibitor (SBTI), ovomucoid and aprotinin do not inactivate ecarin.

Ecarin catalyzes the hydrolytic cleavage of the 323Arg-324Ile bond in the human prothrombin molecule, whereby thrombin activity is generated without the release of any zymogen fragment. This form of active prothrombin has been termed meizothrombin and is inhibited by r-hirudin, PEG-hirudin, and low molecular weight synthetic thrombin inhibitors such as argatroban, but not efficiently by the heparin-ATIII complex.

Ecarin has been used to develop a sensitive analytical method for the determination of thrombin inhibition by the antithrombin drug r-hirudin.^{4,5} The application for this test is to monitor the anticoagulant effect induced in a patient receiving r-hirudin during cardiopulmonary bypass.^{6,9}

The TAS ECT Test Card is based on the method of Nowak and Bucha.⁴ The TAS system is designed to eliminate many of the variables such as transport and handling that are encountered with other coagulation methods.

Principle

The TAS ECT Test Card is a one-stage, two-step test that measures the clotting time of a blood sample. The patient's blood sample is first diluted with pooled normal human plasma. Then, the diluted sample is added to the dry reagent on the prewarmed ECT Test Card. By using ecarin to activate prothrombin, the coagulation cascade (activation of factors V - XIII) is bypassed and a deficiency in one or more of these factors will not be reflected in the result.

Reagent

Components	Storage	Stability
Ecarin calcium chloride, buffers, stabilizers, and paramagnetic iron oxide particles.	2-8°C (36-46°F) 20-25°C (68-77°F)	Unopened—24 months or until expiration date or, Unopened—2 weeks

WARNING: Exposure of the test cards at any time to magnetic objects or fields (for example, an MRI instrument) may corrupt the encoded information and prevent the analyzer from starting the test.

CAUTION: Any pouches not kept refrigerated should be dated and not be used beyond this 2-week period. Pouches should not be repeatedly warmed and returned to the refrigerator. Once the pouch is opened, the card must be used within 15 minutes.

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH:

Inaccurate information on the coagulation status of the patient poses a significant risk to the patient during CPB since both over-treatment and under-treatment can have fatal consequences (bleeding in the patient and clots in the CPB system, respectively). Possible risks of using the TAS ECT Test Card could include underestimation or overestimation of the level of hirudin in the patient. Currently, an antidote for hirudin is unavailable, and the clinical data available are insufficient to establish the probabilities or incidence of erroneous medical judgements and their clinical outcomes.

POTENTIAL BIOHAZARD: All components of this product are of nonhuman origin, and as such, should not contain HBV, HCV, or HIV. Nevertheless, since absence of infectious agents cannot be proven, all samples (e.g., patient blood) and products (e.g., standard and control plasma) obtained from human blood should always be handled with due care, observing the precautions recommended for biohazardous material.^{6,7}

Specimen Collection and Preparation

The TAS ECT Test Card is to be used with citrated whole blood collected and processed according to recognized standards for the handling of blood specimens for coagulation studies.⁷ The blood should be added to either 109 or 129 mmol (3.2% or 3.8%) of the dihydrate form of sodium citrate in a proportion of nine (9) parts whole blood to one (1) part anticoagulant. The blood should be mixed well with the anticoagulant immediately upon collection.

- The citrated whole blood sample must be diluted one to one (1:1) with pooled normal human plasma prior to testing.⁸ Precise pipetting of the sample is important.
- Using a 100 µl pipette, dispense 100 µl of the citrated whole blood into a polypropylene plastic tube.

- SARP (Helena) and FACT (George King) plasmas were used as the pooled normal human plasma for all the ECT studies performed at CVDI. Use of any other pooled normal human plasma may give different results.

- Using the same 100 µl pipette with a new pipette tip, add 100 µl of pooled normal human plasma to the plastic tube containing 100 µl of citrated whole blood. Mix the sample.
- Using a sample transfer device capable of delivering approximately 30-35 µl, transfer 30-35 µl diluted whole blood to the sample test well when prompted by the analyzer.
- Diluted whole blood should be tested within 15 minutes of collection to avoid *ex vivo* changes that may affect the clotting time results.

Materials Required but not Provided

- TAS Analyzer
- TAS Operator Manual
- Pooled normal human plasma
- Blood sampling materials such as venipuncture needles, syringes, alcohol swabs, vacutainer tubes containing sodium citrate
- Sample transfer devices (pipettes with tips or droppers) capable of delivering approximately 30 - 35µl
- Two levels of quality control plasma available from Cardiovascular Diagnostics, Inc.
- 100 µl pipette with tips
- Polypropylene tubes

Directions for Use

1. Equilibrate test cards at room temperature (20 - 25°C) before removing from the foil pouch. No further preparation of the TAS ECT Test Card is necessary prior to beginning the test.
CAUTION: The test card must be used within 15 minutes after the pouch is opened. Pouches of cards should not be repeatedly warmed and returned to the refrigerator.
2. Remove the test card from its foil pouch and hold it so that the full name is right side up, facing you.
3. Pass the test card firmly and steadily through the card reader.
The analyzer interprets the encoded information on the test card and displays prompts for each step of the procedure.
4. When prompted, place the test card in the analyzer, and allow to warm.
CAUTION: Do not leave the test card in the analyzer longer than 15 minutes before applying the sample. Prolonged warming of the card can affect the performance of the test.
5. When prompted, add approximately 30-35 µl of the 1:1 diluted sample into the sample well on the test card.
6. At the end of the test, confirm that the test was performed with the analyzer set to the appropriate sample type. (Sample type is displayed along with the result at the end of each test.)
7. When the card is removed from the analyzer at the end of each test, ensure that the entire reaction chamber was filled with sample. If an inadequate amount of sample was added to the card, repeat the test, using a fresh card.
8. The TAS Analyzer will display the ECT results within 1 to 12 minutes, depending on how long it takes the sample to clot. **CVDI provides no recommendation on dosing of r-hirudin.** The user should dose the patient with r-hirudin in view of the actual medical situation, local experience with the drug, and the pertinent labeling instructions for r-hirudin.
9. Dispose of the test card and other contaminated items in a manner approved for biohazardous materials.

Procedural Notes

- The TAS Analyzer is preset to provide a constant reaction temperature of $37 \pm 3^\circ\text{C}$, and will automatically prewarm the test card before prompting the user to apply the sample drop. All other necessary parameters are magnetically encoded on each test card. Please refer to the TAS Analyzer Operator Manual for details of instrument use.

- Operate the TAS Analyzer only at ambient temperatures between 18 to 32°C.
- To maintain a fully charged battery, leave the unit plugged into its power supply, which is in turn plugged into an AC outlet. Leave the power switch in the "OFF" position while storing the analyzer.
- The Operator Identification Code and the Quality Control Lockout are optional features. Refer to the Operator Manual if either of these features has been enabled.
- Ensure that the sealed pouch containing a test card has reached room temperature and that the TAS Analyzer is either plugged into an appropriate wall outlet or has a sufficiently charged battery.
- Collect and dilute blood in a 1:1 ratio with pooled normal human plasma* as described in the Specimen Collection and Preparation Section.

Quality Control

Calibration: No user calibration is necessary with the TAS ECT Test Card. Calibration of the TAS Analyzer was performed at CARDIOVASCULAR DIAGNOSTICS, INC.

Routine Quality Control Procedures: Prior to each CPB use, the operator should verify that the date and time displayed on the analyzer are accurate. Reset if necessary. (See the TAS Operator Manual for instructions.) This step ensures that the operator will be warned of any attempt to use an expired test card.

The microprocessor in the TAS Analyzer automatically monitors the parameters necessary for accurate testing. If the TAS Analyzer detects an error during the performance of the test, it will display an error message. (See the TAS Analyzer Operator Manual for details and an explanation of error messages.)

At the end of the test, the operator should confirm that the test was performed with the analyzer set to the appropriate sample type. The sample type is displayed along with the result at the end of the test.

When the card is removed from the analyzer at the end of each test, the operator should be sure that the entire reaction chamber (all of the gray area) was filled with sample. If an insufficient amount of sample was added to the card, the test should be repeated, using a fresh card. Dispose of the test card and other contaminated items in a manner appropriate for biohazardous material.

The test card should not be left in the analyzer for longer than 15 minutes before application of the sample. Prolonged warming of the card may affect the performance of the reagent.

Functional Quality Control Testing: Quality control of the total system should be monitored by testing two levels of quality control plasma. Instructions from the manufacturer for reconstitution of these materials must be strictly followed. Both normal and abnormal levels should be run prior to CPB.

Results

The TAS ECT result is reported in seconds and is displayed on the TAS Analyzer screen at the end of the test.

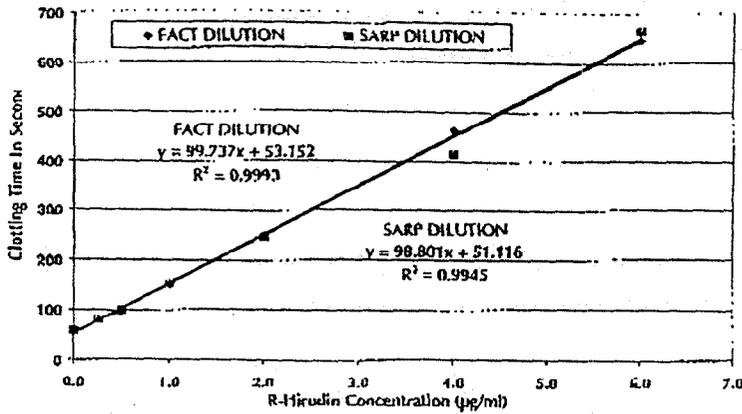
Expected Values

Samples from 120 normal individuals (72 females and 48 males ranging in age from 20 to 63 with a median age of 38) were tested using the TAS Analyzer and TAS ECT Test Cards. Citrated whole blood was diluted 1:1 with pooled normal human plasma. The range (mean \pm 2 S.D.) obtained was 41.6 to 55.3 seconds. This range is given for illustrative purposes only. Results reported as <25 seconds or >700 seconds should be verified by repeat testing.

Fresh citrated whole blood was diluted 30% with phosphate buffered saline (PBS). The PBS/blood mixture was supplemented with various concentrations of r-hirudin and the aliquots were diluted 1:1 with either FACT or SARP plasma, and (five) 5 replicate measurements were performed on TAS-ECT tests (30µl/test).

Results are shown in the graph below. Both FACT and SARP normal pooled plasmas yielded equivalent sensitivity to r-hirudin.

COMPARISON OF TWO DIFFERENT POOLED NORMAL HUMAN PLASMAS ON THE RESPONSE OF TAS ECT TO R-HIRUDIN



Specific Performance Characteristics

Analytical sensitivity

Studies show that the TAS ECT Test Card reagent is sensitive to r-hirudin to 100 ng/mL or 0.1 µg/mL.

Precision

Studies were performed using the TAS Analyzer and TAS ECT Test Cards to evaluate test precision. 4.0 µg/ml was the highest level of r-hirudin used in precision studies, and precision at higher levels of r-hirudin has not been determined. Two levels (0 and 4.0 µg/ml) of r-hirudin were analyzed with citrated whole blood. Aliquots of these samples were then diluted 1:1 with pooled normal human plasma (All precision studies were performed using FACT plasma from George King). The following results were produced.

Within Run Precision

(N = 30 each) These results include instrument to instrument and dilutional precision. Samples for these results were CWB with a 30% PBS dilution.

	0.0 µg/ml r-hirudin:	4.0 µg/ml r-hirudin:
Mean (sec)	55.1	443.4
Std. Dev. (sec)	2.8	27.4
C.V. (%)	5.0	6.2

Operator to Operator Precision

(N = 30 each) These results include instrument to instrument and dilutional precision. Samples for these results were CWB with a 30% PBS dilution.

Operator	0.0 µg/ml r-hirudin:			4.0 µg/ml r-hirudin:		
	1	2	3	1	2	3
Mean (sec)	49.8	50.7	52.2	405.3	396.0	419.2
Std. Dev. (sec)	3.1	2.7	2.6	30.1	22.8	23.1
CV (%)	6.2	5.3	5.0	7.4	5.8	5.5

Day to Day Variation of ECT Test Card

(N = 10 control samples per day for 20 days) These results include instrument to instrument precision.

	Normal Control Range		Abnormal Control Range	
	min	max	min	max
Mean (sec)	52.9	54.7	154.0	159.9
Tot. Precision (S. D.)	2.2		9.2	
Tot. CV (%)	4.1		6.0	

Day to Day Variation of ECT Test Card

(N = 5 samples per day for 20 days) Samples for these results were CWB with a 30% PBS dilution.

	0.0 µg/ml r-hirudin		4.0 µg/ml r-hirudin	
	min	max	min	max
Mean (sec)	55.9	60.6	439.4	529.0
Tot. Precision (S.D.)	4.1		35.5	
Total CV (%)	7.0		6.7	

Day-to-Day Precision – Citrated whole blood samples: Day-to-Day precision was also evaluated (N= 5 samples per day for 20 days) using TAS ECT results compiled from the various preclinical studies performed at Cardiovascular Diagnostics, Inc. These results include Lot-to-lot (total of 6 different ECT lots were used), instrument-to-instrument (at least 5 different TAS analyzers were used each day), and day-to-day precision. Results also include imprecision due to use of multiple donors. These data were analyzed according to "Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline, NCCLS publication EP5-A, Volume 19 Number 2." Total precision standard deviation was 4.1 for citrated whole blood samples with 0.0 µg/ml r-hirudin and 35.5 for citrated whole blood samples with 4.0 µg/ml r-hirudin. Since these data were obtained from multiple TAS analyzers (5), instrument variation was also included in these estimates.

Lot to Lot Precision and Response

R-hirudin (0.0 or 2.0 µg/mL) was added to an undiluted citrated whole blood sample from a normal donor. This sample was evaluated on three lots of TAS ECT Test Cards. Forty replicates were performed for each test card lot.

Lot #	r-hirudin	Mean (sec)	SD (sec)	CV (%)
1	0.0	48.6	2.4	5.0
	2.0	428.6	19.9	4.7
2	0.0	49.3	2.0	4.1
	2.0	397.6	27.8	7.0
3	0.0	48.6	2.0	4.0
	2.0	434.1	25.2	5.8

Results of all the precision testing indicate that the major contribution to imprecision is test-to-test card variation, and not instrument-to-instrument, donor-to-donor, or operator-to-operator.

Interferences

Interference studies were performed on 3.2% citrated whole blood samples or 3.8% citrated plasma samples. These samples were diluted 30% with phosphate buffered saline (PBS, pH 7.3, 50 mM phosphate, 150 mM NaCl) and supplemented with r-hirudin at 0.0 and 4.0 µg/ml. Patient samples containing coumadin (INR ≤ 4.5) should not affect the results of the ECT test. CP samples were used to determine the effect of factor deficiencies on test performance. Less than 30% activity of normal prothrombin (Factor II) will cause prolongation of the ECT. Fibrinogen levels of 15 to 1000 mg/dl have no significant effect on the ECT test results.

CWB samples were used for the following interference tests. Acidified citrate cannot be used to obtain samples for this test. Hematocrits to 64%, lipids to 15 mg/ml, nitroglycerin to 1000 µg/ml, aprotinin to 1000 KIU/ml, dextran to 5 mg/ml, protamine to 100 µg/ml, and sample temperature of 4 to 37°C have no effect on TAS ECT test performance. Unfractionated heparin (UFH) levels below 0.5 U/ml have no effect on test performance. Hemolysis of 25% or less should not effect test performance; however presence of hemolysis is often an indicator of poor specimen quality. Hemodilution greater than 30% causes a statistically significant increase in TAS ECT test results. Plasminogen levels <20% affect ECT test results.

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Cardiovascular Diagnostics, Inc.

Thrombolytic Assessment System (TAS) Ecarin Clotting Time Test

Patient Information

HUMANITARIAN DEVICE:

Authorized by Federal Law for use in determining the anticoagulant effect of recombinant hirudin (r-hirudin) during cardiopulmonary bypass (CPB) in patients who have heparin-induced thrombocytopenia (HIT). The effectiveness of this device for this use has not been demonstrated.

Federal law restricts this device for sale and distribution to, or on the order of, a physician or to a clinical laboratory. Use is restricted to, by, or on the order of a physician.

GENERAL INFORMATION AND PROCEDURES:

The CVDI TAS Ecarin Clotting Time test (ECT) is intended to be used to determine the anticoagulant effect of recombinant hirudin (r-hirudin) during cardiopulmonary bypass (CPB) in patients who have heparin-induced thrombocytopenia (HIT).

The physician uses the results of the TAS ECT test to determine whether the patient has been sufficiently anticoagulated during CPB. This affords the physician the opportunity to adjust the dosage of r-hirudin accordingly.

POSSIBLE BENEFITS AND RISKS OF USING THE TAS ECT TEST:

The potential benefit of using the TAS ECT test is that r-hirudin therapy can be guided using TAS ECT test results. Possible risks include:

- under- or overestimation of r-hirudin levels in patients leading to bleeding or clotting episodes, and
- inaccurate information on coagulation status in patients.

ALTERNATIVE PRACTICES AND PROCEDURES

Currently, the performance of *in vitro* diagnostic coagulation procedures, such as the activated partial thromboplastin time (aPTT), activated clotting time (ACT) and the prothrombin time (PT) tests has not been established for monitoring r-hirudin at the levels necessary during CPB.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: June 21, 2000
From: Humanitarian Device Exemptions (HDE) Staff, ODE, CDRH
(HFZ-403)
Subject: HDE Approval Package (H990012)
To: Dockets Management Branch (HFA-305)

Attention:

Lyle Jaffe
Jennie Butler
Gloria Ortega

The following HDE application was recently approved:

HDE Number: H990012
Docket Number: 00M-1354
Device Name: TAS Ecarin Clotting Time Test
Applicant: Cardiovascular Diagnostics, Inc.

Attached is the following information for this HDE:

Approval Order
Summary of Safety and Probable Benefit
Labeling

If you have any questions, please call me at (301)594-1190
ext. 107.

Marsha Melvin

Marsha Melvin

Attachments

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