DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

APR 6 1998

Mr. William H. Duffell
Regulatory Affairs
Cobe BCT, Inc.
1201 Oak Street
Lakewood, Colorado 80215-4498

Re: H970004
Excorim® Immunoadsorption System
Filed: October 23, 1997
Amended: January 14, February 5, March 3, 6, 12, 26, and 27, 1998.

Dear Mr. Duffell:

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 Excorim® Immunoadsorption System. This device is indicated for use in the treatment of patients with hemophilia A and B who have Factor VIII or Factor IX inhibitor titers above 10 Bethesda Units/ml (BU/ml). The purpose of the system is to lower the inhibitor levels so that routine clotting factor replacement therapy can be considered. It may be used in an acute setting (to control bleeding during an acute hemorrhage or for emergency surgery) or as a preventative measure to prepare patients for elective surgery. 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 upon receipt of this letter.

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 (1) the labeling shall specify the training requirements for practitioners who may use the device as approved in this order and (2) the sale, distribution, and use must not violate sections 502(q) and (r) of the act (21 U.S.C. 352(q) and (r)).

In addition to the above, an FDA inspection must find that your manufacturing facilities, methods, and controls for this device comply with the applicable Current Good Manufacturing Practice requirement, as set forth in the Quality System Regulation (QS) for Medical Devices; General regulation (21 CFR Part 820). Such an inspection will be scheduled and conducted by your District Office. If you have any questions regarding the status of your GMP inspection, please contact your District Office or the Office of Compliance, CDRH at (301) 594-4695.

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/hdeinfo.html. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. 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.

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 Miriam C. Provost, Ph.D. at (301) 594-1220.

Sincerely yours,

Kimber C. Richter

Kimber C. Richter, M.D.
Deputy Director
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 -

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(c)(2), (c)(3), and (c)(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 "Request for Extension of HDE Approval" 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

I. GENERAL INFORMATION

Device Generic Name: Extracorporeal immunoadsorption system

Device Trade Name: Excorim® Immunoadsorption system

Applicant's Name and Address:

Cobe BCT, Inc.
1201 Oak Street
Lakewood, CO 80215-4498

Humanitarian Device Exemption (HDE) Number: H970004

Date of Humanitarian Use Device Designation: November 14, 1996

Date of Panel Recommendation: The HDE was not reviewed by an FDA advisory panel. However, a previous premarket approval (PMA) for a similar device (i.e., the IMRE Prosorba® column) for a different indication was reviewed by the Gastroenterology/Urology panel on July 29, 1986. Therefore, it was determined that the application substantially duplicates information previously reviewed by the advisory panel.

Date of Good Manufacturing Practices inspection: A pre-approval inspection for the HDE was not performed. However, a routine GMP inspection was performed on April 21, 1997 and no deficiencies were noted.

Date of Notice of Approval to Applicant: APR 6 1998

II. INDICATIONS FOR USE

The Excorim® Immunoadsorption system is indicated for use in the treatment of patients with hemophilia A and B who have Factor VIII or IX inhibitor titers above 10 Bethesda Units (BU)/ml. The purpose of the system is to lower the inhibitor levels so that routine clotting factor replacement therapy can be considered. It may be used in an acute setting (to control bleeding during an acute hemorrhage or for emergency surgery) or as a preventative measure, to prepare patients for elective surgery.

III. DEVICE DESCRIPTION

The Excorim® Immunoadsorption system consists of the following components:

- **Immunosorba Protein A columns**

  The Immunosorba columns contain Protein A covalently immobilized to a Sepharose ® support matrix. Protein A is a 42 kD molecular weight protein synthesized by *Staphylococcus aureus*. It is an affinity ligand for binding IgG and to a lesser extent, IgM and IgA. Each column contains 62.5 ml of the Protein A-Sepharose® adsorbent and is capable of binding 1.2 g of immunoglobulin when fully saturated. The column housing is composed of polycarbonate and contains polypropylene filters (36 μm) at either end. Connectors are made of polyvinylchloride (PVC). The column is 5 cm long and 4 cm in diameter and has a priming volume of 72.5 ml. Two columns are used during each treatment.

- **Citem® 10 Monitor plus accessories**

  The Citem® 10 monitor is designed to monitor and control treatment with the Immunosorba® columns. After the first column is saturated by immunoglobulin, the Citem® 10 automatically switches flow to the second column. It then rinses residual plasma from the column using Buffer PA solution and regenerates the column by elution with Eluant PA, a low pH solution. The elution step is followed by flushing with Buffer PA solution to readjust the pH and prepare it for resumption of plasma flow. In this fashion, cycles of adsorption and elution alternate between the columns throughout the depletion procedure every 7 or 10 minutes.

  The Citem® 10 monitors the pH and protein concentrations of the fluid leaving the columns. Switching valves direct the fluid leaving the column along one of three paths (i.e., plasma return line, waste fluid line, fraction line). The valves are microprocessor controlled and respond to signals from the detectors. The detectors include a pH electrode, two optical density detectors and one UV detector. The amount of plasma processed and the volume of plasma returned to the patient is continuously monitored.

  The Citem® 10 includes alarms to monitor the following: (1) air in the inlet lines to the columns, (2) pressure at the column inlet, and (3) pH of the plasma returning to the patient. The air and pressure alarms are programmed to stop all pumps immediately whenever they are triggered. The pH alarm will cause the plasma to divert to the waste bag for one minute. If there is no operator response within one minute, pumps are automatically stopped to prevent low pH plasma from returning to the patient.

  The Citem® 10 also includes a stand with the following accessories:

(1) column holder grip, (2) upper and lower holder for bag pole, (3) bag pole, (4) bag holders, (5) label, and (6) mounting hardware.

- **Excorim® medical lines, including inlet line, outlet line, Cobe Spectra® connection lines, waste bag, double bag, and fraction bag**

  The medical lines are designed specifically for use with the Excorim® Immunoadsorption system. All patient contacting components of tubing sets, bags and fittings are made of PVC. They are sterile, disposable and for single use only.

- **Disposable pH electrode**

  The pH electrode monitors the pH of the fluid returned to the patient. The electrode is sterile, disposable and for single use only. It has a range of 2-8 pH units and an accuracy of $\pm$ 0.1 pH unit.

- **Buffer PA and Eluant PA solutions for flushing and regeneration of the columns**

  Buffer PA is a sterile solution with a pH of 7.0. It is packaged in 1 liter PVC bags. It is used for flushing the Immunosorba® columns and for returning plasma to the Cobe Spectra™ for eventual return to the patient. The solution has the following composition:

Trisodium citrate (dihydrate)	3.30 g/1 L
Sodium acetate (trihydrate)	5.45
Sodium chloride	4.90
Disodium hydrogen phosphate (dodecahydrate)	2.91
Potassium dihydrogen phosphate	0.26

pH adjustment with hydrochloric acid or sodium hydroxide

  Eluant PA is a sterile solution with a pH of 2.2. It is packaged in 1 liter PVC bags. It is used to elute the bound immunoglobulin from the Protein A-Sepharose® adsorbent during the column regeneration procedure. The solution has the following composition:

Citric Acid (monohydrate)	6.12 g/1 L
Sodium chloride	9.00

pH adjustment with hydrochloric acid or sodium hydroxide

- **Thimerosal 10% solution for preservation of the columns**

  This solution is a sterile 10% solution of thimerosal (merthiolate). It is supplied

in 10 ml glass bottles. A diluted solution of thimerosal is used to preserve the Immunosorba® columns between procedures. The diluted preservative solution is prepared by mixing 10 ml of thimerosal 10% in 1 L Buffer PA.

Device Operation

The Excorim® Immunoadsorption system is designed to continuously remove immunoglobulin from the plasma of hemophilia patients. To use the device, the patient's blood must first be separated using the Cobe Spectra™ Apheresis system. After treatment by the Excorim® system, the plasma is sent back to the Cobe Spectra™ for return to the patient. The Excorim® system functions as follows:

Initial Setup

The Immunosorba® columns are preserved with a 0.1% thimerosal solution. The initial setup procedure rinses this solution from the columns with successive washings of 300 ml of Buffer PA solution, 100 ml of Eluant PA solution, and another 350 ml of Buffer PA solution. The columns are then ready for the treatment phase.

Treatment Phase

The separated plasma is pumped through one of two Immunosorba® columns where the immunoglobulins are bound to the Protein A-Sepharose® adsorbent. Plasma flow rates may be set between 7 and 50 ml/min. After a specified cycle time, the plasma flow is switched to the second Immunosorba® column, where removal of the immunoglobulins continues. During this time, the first column is being regenerated according to the procedure described below. Plasma is cycled from one column to the other every 7 or 10 minutes during this phase.

Regeneration

Regeneration is accomplished by first rinsing out the remaining plasma with 90 or 108 ml of Buffer PA solution, followed by lowering of the pH by perfusion with 90 or 108 ml of Eluant PA solution. Eluant PA, a low pH solution, releases bound immunoglobulins from the Protein A-Sepharose® adsorbent. Following perfusion with Eluant PA solution and removal of immunoglobulins, the column is returned to its initial condition by washing with 120 or 133 ml of Buffer PA solution. (In each case, the lower volume of fluid is used for the 10 minute cycle and the higher volume of fluid is used for the 7 minute cycle.)

Storage

At the end of each procedure, the columns are regenerated and then filled with 0.1% thimerosal solution for disinfection and preservation. The columns are stored in a refrigerator and are reused by the same patient throughout a treatment course, which may consist of multiple depletion procedures over a series of days.

IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

The Excorim® Immunoadsorption system is contraindicated for the following conditions:

- Patients for whom adequate anticoagulation with acid citrate dextrose (ACD) either alone or in combination with heparin, cannot be maintained.
- Patients who are receiving angiotensin converting enzyme (ACE) inhibitors.
- Patients with cardiovascular and/or pulmonary disease of such a degree that extracorporeal therapy is not permissible.
- Patients with sepsis.
- Patients with a known allergy to Protein A or Staphylococcus-derived products.
- Patients with a known allergy or sensitivity to thimerosal (merthiolate).

The Warnings and Precautions can be found in the Professional Labeling (Attachment 1).

V. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The adverse effects that were observed during clinical evaluation of the Excorim® Immunoadsorption System include transient episodes of nausea and vomiting, fever, chills, numbness, tingling, paresthesia, pain, cramps, headache, dyspnea, tremor, dizziness and changes in blood pressure and heart rate. These effects have been observed with other extracorporeal procedures, especially when citrate anticoagulant and immunosuppressive or cytotoxic drugs are used concomitantly. Other potential complications which were not seen during clinical evaluation include blood or plasma loss from leaks, bleeding or clotting from improper anticoagulant use, fluid balance mismanagement and sepsis.

In addition to removal of IgG, the column also removes lesser amounts of IgA, IgM, IgE and albumin. Although no adverse effects were noted due to depletion of these factors, there is a theoretical risk of infection due to immune suppression.

During the clinical evaluation of the device, there were several patients with very high inhibitor levels for whom multiple procedures failed to reduce inhibitor levels below 10 BU/ml. Therefore, there is a risk that treatment with this device may not produce the desired outcome (i.e., lowering of inhibitor levels below 10 BU/ml). If this occurs, there is a theoretical risk of uncontrollable bleeding at the blood access sites if hemostasis cannot be achieved.

VI. ALTERNATE PRACTICES AND PROCEDURES

For patients with low inhibitor levels (less than 10 BU/ml) replacement therapy using the missing coagulation factor is usually sufficient to achieve hemostasis. For patients with inhibitor levels greater than 10 BU/ml, however, treatment with replacement factor, even in high doses, is usually not effective.

Plasmapheresis has been shown to transiently reduce inhibitor levels and allow hemostasis to be achieved in some patients.[1] However, plasmapheresis is seldom used because it is limited to 1 or 1.5 plasma volume exchanges which results in an ineffective lowering of inhibitor levels. In addition, electrolytes, clotting factors, fibrinogen and other plasma proteins are also reduced. Plasmapheresis is not specifically indicated for treatment of hemophilia patients with high levels of inhibitors.

Prothrombin complex concentrates have been shown to stop hemorrhage in some patients[2]. However, they were found to be effective in only 50% of the bleeding episodes. The cessation of bleeding episodes was increased to 60 to 65% by utilizing activated prothrombin complex concentrates[3]. Recombinant Factor VIIa has also been found to stop hemorrhage in some patients[4-5]. Porcine Factor VIII has also been used, however, cross-reactivity can occur.[6]

In summary, there is no other device available specifically for the treatment of patients with hemophilia A and B who have Factor VIII or Factor IX inhibitor levels above 10 BU/ml.

VII. MARKETING HISTORY

The Excorim® Immunoadsorption system has been marketed in Europe for approximately 10 years for the treatment of various diseases and disorders, including hemophilia. The other diseases for which the device was used are immunological in nature. Table 1 lists the countries where the Excorim® Immunoadsorption system has been used, the date marketing was approved and the amount of product distributed as of June 11, 1996.

The total number of patients treated with Excorim® Immunoadsorption system is 1,080. No cases of product withdrawal, either by a governing body or voluntarily by a distributor, are known.

Table 1. Countries where Excorim® Immunoadsorption Systems have been marketed, the number of units supplied and the number of patients treated.

Country	*Date of Marketing*	*Number of Citem® 10 Monitors distributed*	*Number of Immunosorba® columns distributed*	*Number of patients treated*
Sweden	**10/85**	**9**	**584**	**292**
Norway	**5/87**	**2**	**64**	**32**
England	**7/86**	**12**	**264**	**132**
France	**9/87**	**7**	**142**	**71**
Spain	**11/87**	**4**	**122**	**61**
Italy	**1/88**	**14**	**478**	**239**
Israel	**---**	**0**	**8**	**4**
Republic of China	**7/86**	**1**	**2**	**1**
Denmark	**8/89**	**2**	**12**	**6**
Germany	**6/91**	**15**	**314**	**157**
Belgium	**5/95**	**2**	**6**	**3**
Austria	**1/94**	**3**	**58**	**29**
Russia	**10/94**	**1**	**80**	**40**
Poland	**1/95**	**1**	**6**	**3**
Croatia	**9/94**	**1**	**10**	**5**
Slovenia	**9/94**	**1**	**10**	**5**

VIII. SUMMARY OF PRE-CLINICAL STUDIES

A. Performance of Immunosorba® Protein A columns

The effectiveness of the Immunosorba® columns for removal of IgG was verified through a series of *in vitro* tests. Testing was done using human plasma at flow rates that simulated the anticipated clinical usage of the columns. The testing demonstrated the following:

1. Each column has a capacity for IgG of > 1.2 g. In a simulated treatment with 2000 ml of plasma, 92.9% of IgG was removed after repeated cycles of adsorption and regeneration.

2. The Immunosorba® column has a lower affinity for IgM and IgA. In simulated treatments with 80 ml of plasma, the system removed 35-40% of the IgA and 50-60% of the IgM.

3. During treatment with the Excorim® Immunoadsorption System, some albumin loss was observed due to dilution effects at the beginning and the end of each cycle. The albumin loss was measured in two different experiments and ranged from 5 to 11 percent.

4. The system provides a nearly complete plasma balance. This was verified by conducting a simulated treatment in which three plasma volumes were processed in six consecutive depletion procedures on five pairs of columns. The results showed a plasma volume change of +2 to -3 percent.

5. The column was not shown to irreversibly bind any proteins. This was verified by analyzing the Protein A-Sepharose® adsorbent in 8 different columns after saturating the column and then eluting the bound proteins. No evidence of bound proteins was observed after the elution procedure.

B. Safety of Immunosorba® Columns

The safety of the Immunosorba® columns was evaluated in a series of *in vitro* experiments. The experiments demonstrated the following:

1. No Protein A was observed to leach from the columns after a single use provided the columns were first flushed with 600 ml of Buffer PA. No additional Protein A was observed to leach from columns after repeated cycles of adsorption and regeneration.

2. Staphylococcal Protein A is often contaminated with small amounts of Staphylococcal enterotoxin A (SEA) and enterotoxin B (SEB). Two different lots of purified Protein A were analyzed and were found to contain less than 0.1 μg of SEA/g Protein A.

3. No agarose (from Sepharose®) was observed to leach from the columns when contacted with 120 ml of saline at 10 ml/min.

4. Extracts from the columns meet British Pharmacopoeia standards for large volume parenterals for particles of size > 2 μm and > 5 μm and USP XXII standards for large volume parenterals for particles of size > 10 μm and > 25 μm.

C. Safety of Regeneration and Preservation Procedures for Immunosorba® Columns

1. To investigate the performance of columns after repeated regeneration cycles, a "mini column" was developed that had similar flow characteristics to the Immunosorba® column. The column was used for 99 cycles of adsorption and elution, with periodic testing of the binding capacity of the Protein A-Sepharose® adsorbent. Seven rounds (of 99 cycles each) were investigated. The results show minimal changes in the binding capacity of the column, even after 699 cycles.

2. The Immunosorba® columns are preserved in between treatments with a solution of 0.1% thimerosal. Thimerosal is a mercury compound with bactericidal and sporostatic properties. A study was conducted to determine the potential leakage of thimerosal to the patient with each procedure. Fourteen columns were tested, with each one undergoing 6 procedures (a total of 7.5 L of plasma was recirculated for each procedure.) Samples were taken periodically and analyzed for mercury. No correlation was found between the amount of mercury transferred and the number of times that the column had been regenerated, indicating that the columns do not release more thimerosal after repeated regeneration cycles. The mean transfer of mercury is 22 μg per each procedure of 3 plasma volumes (i.e., 7.5 L).

D. Pre-clinical testing of solutions: Buffer PA and Eluant PA

All chemical components of Buffer PA solution and Eluant PA solution meet either U.S. or European Pharmacopoeia standards for purity. Each batch of solution is evaluated for chemical analysis, sterility and pyrogenicity.

E. Pre-clinical testing of solutions: Thimerosal (10%)

The antimicrobial effect of a 0.1% thimerosal solution was evaluated with the following organisms: *A. niger C. albicans, E. coli, P. aeruginosa, and S. aureus*. Samples of Thimerosal (10%) were filtered and diluted with 1 L of Buffer PA prior to use. Testing was performed according to USP XXII. Samples were taken at 0, 12 and 24 hours and 4, 7, 14, 21 and 28 days. At time zero, each sample was inoculated with 10^5 colony forming units (CFU). For *E. coli* and *S. aureus,* no organisms were detected after 24 hours. For *P. aeruginosa*, no organisms were detected after 24 hours,

with the exception of one sample, which still showed 12 CFU/ml after 4 days. For *C. albicans*, no organisms were detected after 14 days. For *A. niger*, no reduction in CFU were observed, however, no increase was observed, either. The data indicated that the 0.1% thimerosal solution does have an antimicrobial effect on bacteria and yeast. For fungi, it acts as a fungistatic agent.

F. Pre-clinical testing of Excorim® Medical Lines

The Excorim® Medical lines use components, bonds and manufacturing techniques similar to the industry standard for blood lines used for hemodialysis. In particular, these lines are similar to blood lines previously reviewed by FDA under two premarket notification submissions (K770691 and K801016). The medical lines are 100% leak tested during manufacturing, however, joint separation and flexural strength testing has not been conducted. Since these lines have been in clinical use for approximately ten years without reports of medical safety issues, and due to the similarity of these lines to other FDA-cleared blood lines, the limited pre-clinical testing is acceptable.

The Double, Fraction, and Waste bags are subjected to leak and pressure testing during manufacturing. The Waste bag is underwater-leak tested at 0.3 bar for 10 seconds, the Double bag is pressure tested (between plates with a distance of 30 mm) at 0.7 bar for 60 seconds, and the Fraction bag is underwater-leak tested at 0.4 bar for 15 seconds and pressure tested at 2.1 bar for 60 seconds. The leakage rate for these tests is less than 0.001%.

G. Pre-clinical testing of the Citem® 10 Monitor

1. Software

   Testing of the software for the Citem® 10 monitor included modular-, integrated-, and system-level tests conducted throughout the development of the software. In addition, verification and validation tests and a system-level hazard analysis were performed on the finished device at the end of the development process. The results of the software testing showed that the software performed according to the established design specifications and that the design was appropriate for this intended use.

2. Functional Tests

   Functional testing was performed to evaluate the volume and flow control, pressure detection, column air detector, plasma and

ultraviolet (UV) optical detection, pH detection, and technical alarms. The results demonstrated that the detectors performed according to the established design specifications. Testing also demonstrated that the Citem® 10 monitor responded to a hazard condition in a safe manner (e.g., pumps shut off, return line clamped) and that all alarms operated satisfactorily.

3. Electrical Safety

The Excorim® Immunoadsorption System was designed and tested to comply with IEC 60601-1. The results of the tests showed that the device met the safety requirements of this standard.

4. Electromagnetic Compatibility (EMC)

The Excorim® Immunoadsorption System was designed and tested to comply with IEC 60601-1-2. The results of the tests conducted, and the inclusion of a precaution in the device labeling regarding radiated emissions, supports the safe performance of the system as related to EMC.

5. Disposable pH electrode

The disposable pH electrodes have been tested for accuracy of pH measurements with standardized solutions. Testing has demonstrated adequate performance after sterilization and storage.

H. Biocompatibility of patient-contacting components

1. The housing for the Immunosorba® column is composed of polycarbonate. The internal filters, ports, caps and connectors are composed of silicone rubber, polypropylene, Acryl-butadiene-styrene and PVC. All of these materials are well-characterized and are often used to fabricate the disposable components for extracorporeal systems. The biocompatibility of these materials has been demonstrated by the following tests: intracutaneous irritation, acute systemic toxicity, hemolysis and cytotoxicity.

2. Buffer PA and Eluant PA solutions are packaged in polyvinylchloride (PVC) bags. The plastic in these bags was formulated to meet British Department of Health specifications for containers for human blood, blood components and aqueous solutions for intravenous perfusion. The bags were tested to meet

USP Class VI, and extracts were shown to pass the MEM elution cytotoxicity test and acute systemic toxicity testing (mouse model).

3. Studies were performed to evaluate the presence of toxic or irritant leachables from the Protein A-Sepharose® adsorbent. Nine Immunosorba® columns were extracted with saline that was recirculated through the columns for 24 hours at 37 °C. The extracts were tested for cytotoxicity, acute systemic toxicity, intracutaneous toxicity, hemolysis and genotoxicity (Ames assay). The extracts were shown to be negative for all tests.

4. Additional testing was performed to evaluate the acute and chronic toxicology of Protein A and Protein A-Sepharose® when administered intravenously to rats. In the acute test, six rats per group were given 0.1, 1.0 and 10 mg Protein A per kg body weight. Rats were observed for 14 days and a gross necropsy was performed at the end of the study. The females in the high dose group showed pilo-erection and decreased locomotor activity during the first four hours after injection. All other observations were normal. In the chronic test, 24 rats (12 males and 12 females) were given extracts of Protein A-Sepharose® intravenously for 32 days (dose of 10 ml/kg). No mortalities or clinical signs were observed as compared to the control group. At necropsy, there were no pathological or histological findings.

5. The patient contacting components of the Excorim® medical lines are composed of PVC. This material is well-characterized and is often used to fabricate the disposable components for extracorporeal systems . Biocompatibility testing has been performed on all tubing materials used in the Excorim® medical lines, in accordance to FDA's Blue Book Memo, G95-1, with the exception of the sensitization test, which has been omitted. However, as mentioned earlier, the Excorim® Medical Lines have been used in Europe for approximately 10 years with no reported medical safety issues. Additionally, physico-chemical tests, such as heavy metal concentrations. UV absorption, and characterization of residuals, have been performed. The test results demonstrated adequate biocompatibility.

I. Shelf life testing

1. Immunosorba® columns

The Immunosorba® columns are labeled with a 12 month shelf life. To validate this shelf life, nine columns from two different

lots were stored at 2 to 8 °C (the recommended storage temperature). The columns were sampled at 6 and 12 months and analyzed for the following: visual inspection, effluent pH, sterility, particulates, pyrogenicity, leaching of Protein A, IgG binding and pressure/flow characteristics.

All nine columns demonstrated acceptable stability for all parameters after 12 months of storage, with the exception of the visual inspection. One column failed visual inspection at 6 months and four columns failed visual inspection at 12 months. The failures were attributed to a manufacturing defect which has since been corrected.

2. Excorim® medical lines

The Excorim® Medical Lines will be labeled with a manufacturing date. An expiration date will not be included.

3. Disposable pH electrode

The expiration date for the pH electrode is 12 months after production. Stability testing on these electrodes has been performed. Devices were stored 3 to 18 months at room temperature, and analyzed for sterility, microbial integrity, and pH of the electrode storage solution. In addition, an accelerated study was performed using 12 pH electrodes stored for 2 months at 40°C. In both cases, the pH electrodes were shown to remain sterile and to perform adequately after storage.

4. Buffer PA, Eluant PA and Thimerosal (10%) solutions

Buffer PA and Eluant PA solutions are labeled with a 3 year (36 month) shelf life. To validate this shelf life, samples from one lot were stored at room temperature and were analyzed for sterility, pyrogenicity, particulate matter, pH, and chemical identity. Buffer PA solution passed all tests. Eluant PA solution also passed all tests, with the exception of the analysis for citric acid. Two of the three samples were found to be outside the accepted range at 12 months, however, subsequent samples (taken at 18, 24 and 36 months) were within the acceptable range.

The Thimerosal (10%) solution has a shelf life of 18 months. Stability was investigated by visually examining bottles of Thimerosal 10% solution for crystal formation after 0, 1, 3 and 6

months. Crystals were found after 6 months of storage. In a second test, samples were evaluated after storage for 0, 3, 6, 9, 12 and 18 months for visual appearance and antimicrobial effectiveness (according to USP XXII). Crystals were found after six months of storage, however, the solution still passed the antimicrobial effectiveness test, demonstrating acceptable performance after storage.

J. Sterility testing

The Protein A-Sepharose® adsorbent in sterilized by electron beam radiation with a minimum dose of 2.5 Mrad and a sterility assurance level of 10^{-6}. The column housing set (consisting of an empty Immunosorba® column housing connected to PVC tubing) is sterilized with ethylene oxide. The sterility assurance level is 10^{-6}. The levels of residuals are less than 25, 25 and 250 ppm for ethylene oxide, ethylene chlorohydrin and ethylene glycol, respectively. The column housings are then aseptically filled with the previously sterilized Protein A-Sepharose® adsorbent. Prior to release, the column housing sets are tested for particulates, sterility and pyrogenicity (in addition to a visual inspection).

The disposable pH electrodes are sterilized with gamma radiation with a nominal dose of 34.7 kGy. This ensures a minimum dose (within a 95% confidence interval) of 25 kGy. The sterility assurance level is 10^{-6}. Testing for pyrogenicity is performed prior to release using the rabbit test.

The Excorim® medical lines are sterilized with ethylene oxide. The sterility assurance level is 10^{-6}. The levels of residuals are given as less than 25, 25, and 250 ppm for ethylene oxide, ethylene chlorohydrin and ethylene glycol, respectively. Prior to release, the product is tested for sterility, pyrogenicity and ethylene oxide residuals.

Buffer PA and Eluant PA are steam sterilized with a sterility assurance level of 10^{-6}. Prior to release, the solutions are analyzed for sterility and pyrogenicity. The sterility assurance level is 10^{-6}.

Thimerosal (10%) is filtration sterilized (using a 0.22 μm filter) and aseptically filled into sterile 10 ml glass bottles and capped with sterile silicon rubber stoppers. The sterility assurance level of the solution is 10^{-3}. The glass bottles are sterilized by dry heat (160 °C for 2 hours) and the silicon rubber stoppers are sterilized by steam (121 °C for 15 minutes). Prior to release, the solution is analyzed for sterility according to the USP.

IX. SUMMARY OF CLINICAL STUDIES

A. U.S. Hemophilia Study

A study was performed to evaluate acute removal of immunoglobulins from the plasma of hemophilia patients in whom clinically significant titers of antibodies against Factor VIII or IX had been demonstrated. The study was performed at 13 sites in the United States. Twenty-two patients were enrolled. Of these 22 patients, there were 19 males and 3 females, and the average age was 44. Thirteen patients had congenital hemophilia and 9 had acquired hemophilia. Nineteen patients had Factor VIII deficiency, 1 had Factor IX deficiency and 2 had other coagulation disorders. The study had the following inclusion/exclusion criteria:

Inclusion criteria

- Patient's inhibitor level exceeded 10 BU
- Patient had a documented anamnestic response
- Patient presented with one of the following: (1) Acute bleeding (2) Need for surgery (3) Recurrent, disabling bleeding.

Exclusion Criteria

- Pregnancy
- Active bacterial infection
- Active hepatitis or acquired immunodeficiency syndrome (AIDS)
- Patient unable to give informed consent
- Age over 70
- Weight under 40 kg

Deviations from protocol

Four of the 22 patients had inhibitor levels less than 10 BU/ml upon enrollment. Two patients were over 70 years of age, one patient's weight was under 40 kg, and one patient had active hepatitis or AIDS.

Treatment Schedule

Each treatment consisted of a series of individual depletion procedures that were performed consecutively. A total of 22 patients were evaluated which constituted 25 treatments, and 87 depletion procedures. Typically 3.1 plasma volumes were processed for each depletion procedure and each treatment consisted of 3.5 depletion procedures. The mean number of plasma volumes treated over the entire treatment was 10.2.

The reason for enrollment is available for 23 of the 25 treatments. Of these 23 treatments, 13 were for patients experiencing acute bleeding. Seven of these 13 treatments were for patients who were also described as being disabled by recurring bleeding. An additional 6 treatments were provided to patients described only as disabled by recurring bleeding. Four treatments were provided to patients who required unavoidable surgery.

Effectiveness Evaluations

For the 22 patients, the mean percent reduction in IgG, Bethesda Unit (BU), IgM, IgE, IgA and albumin are shown in Table 2. . Only 20 patients with Factor VIII and Factor IX inhibitors are included in the results for Bethesda Unit reduction.

Table 2. Average Mean Percent Reduction observed over entire treatment course in U.S. Hemophilia Study

	Mean Percent Reduction	Standard Deviation	Number of Treatments*	No. of Patients†
BU	81.0	19.7	19	18
IgG	76.2	23.2	24	21
IgM	50.7	26.1	23	20
IgE	42.0	48.7	8	8
IgA	39.2	18.2	23	20
Albumin	22.8	11.0	14	13

**Number of treatments for which data are available.* *†Number of patients for which data are available.*

The 25 treatments consisted of from 1 to 7 depletion procedures. As shown in Tables 3-4, the mean pre-treatment values for IgG and BU show a declining trend from the first depletion procedure. Regardless of the initial concentration, the Excorim® Immunoadsorption system was shown to lower IgG by approximately the same mean percent change for each depletion procedure.

Table 3. Reduction in IgG observed per depletion procedure during U.S. Hemophilia study with Excorim® Immunoadsorption System.

Depletion Procedure No.	*No. of Patients†*	*No. of Treatments‡*	*Pre (mg/ml) Mean ± SD (N)*	*Post (mg/ml) Mean ± SD (N)*	*Mean Percent Change*
1	22	25	13.39 ± 8.10 (25)	5.12 ± 4.99 (24)	67.9 ± 16.8 (24)
2	21	24	8.04 ± 5.69 (24)	3.60 ± 3.22 (22)	59.5 ± 22.3 (22)
3	16	16	6.82 ± 3.75 (16)	3.05 ± 2.93 (15)	59.9 ± 19.2 (15)
4	10	10	6.59 ± 4.29 (10)	2.70 ± 2.37 (9)	63.4 ± 16.3 (9)
5	7	7	7.56 ± 5.32 (6)	2.54 ± 2.36 (7)	66.5 ± 9.2 (6)
6	4	4	2.82 ± 1.12 (3)	1.06 ± 0.54 (4)	56.9 ± 29.2 (3)
7	1	1	5.40 (1)	n/a*	n/a*

** Values not measured. † Number of patients for which data are available. ‡ Number of treatments for which data are available.*

Table 4. Reduction in BU observed per depletion procedure during U.S. Hemophilia study with Excorim® Immunoadsorption System.

Depletion Procedure No.	*No. of Patients†*	*No. of Treatments‡*	*Pre (BU/ml) Mean ± SD (N)*	*Post (BU/ml) Mean ± SD (N)*	*Mean Percent Change*
1	20	22	882 ± 2848 (21)	93 ± 190 (22)	66 ± 25 (21)
2	19	21	401 ± 1167 (21)	97 ± 257 (21)	69 ± 23 (21)
3	15	15	230 ± 466 (15)	132 ± 383 (15)	69 ± 23 (15)
4	9	9	431 ± 941 (9)	25 ± 34 (8)	75 ± 20 (8)
5	7	7	656 ± 1124 (6)	155 ± 255 (5)	79 ± 9 (5)
6	4	4	452 ± 488 (4)	235 ± 410 (4)	69 ± 29 (4)
7	1	1	2200 (1)	n/a*	n/a*

** Values not measured. † Number of patients for which data are available. ‡ Number of treatments for which data are available.*

As shown in Table 5, follow-up data on clinical outcomes is available on 13 of the 22 patients. The investigators reported that bleeding was stopped or surgery was successful in nine of the 13 patients for which follow-up data was available. Bleeding was not resolved for two patients. For another two patients, therapeutic levels of coagulation factor were achieved, however, no information is available on whether bleeding was stopped or surgery was successful.

Table 5. Follow-up data on clinical outcomes for U.S. Hemophilia study with Excorim® Immunoadsorption System.

Patient Number	Presented to stop bleeding	Presented to establish factor level prior to surgery	Presented to induce immune tolerance	BU lowered to less than 10/ml	Therapeutic level of factor achieved	Bleeding stopped or surgery successful	Bleeding not resolved
1	X	X		X	X	X	
2			X	X	X		
3	X			X	X		
4	X			*			
5		X	X	X			
6	X						
7	X			X			
8		X		X	X	X	
9	X			X			
10	X						
11	X					X	
12	X						
13	X					X	
14	X						
15	X			X			
16	X			X		X	
17	X			X			X
18	X						X
19	X					X	
20	X			*		X	
21	X			X		X	
22		X		X		X	
Total	18	4	2	12	4	9	2

*Patients had other coagulation disorders, not measurable by Bethesda Units

Safety Evaluations

There were six deaths reported by physicians conducting this study. The causes of death are listed below. None of the deaths were attributed to the use of the device.

1. Patient's death was attributable to the development of pneumonia as a consequence of chronic lymphocytic leukemia.
2. Patient's death was attributable to congestive heart failure.
3. Patient's death was due to a seizure as a result of meperidine administration for analgesia.
4. Patient's death was attributable to acute internal bleeding.
5. Patient's death was due to a massive hemothorax and respiratory distress due both to the collapse of the right lung and focal interstitial pneumonitis.
6. Patient had multiple contributory causes to his death which included upper & lower gastrointestinal bleeding, *Staphylococcus* sepsis, middle lobe pneumonia, disseminated intravascular coagulation, and intracranial hemorrhage.

The adverse events observed during the study are shown in Table 6. Many of these reported adverse events can be experienced by patients during any extracorporeal procedure. No depletion procedure was discontinued prematurely due to any of these adverse events. In addition, the following adverse events were recorded during follow-up visits: nausea (1), tingling (1), lightheadedness (1), thrombocytopenia (2), oozing from venous catheter insertion site (1).

No infectious complications were attributed to the procedure, although one patient had a positive blood culture for coagulase negative *Staphylococcus*. The patient later died of multiple causes.

All patients enrolled in the study were subjected to a panel of standard laboratory tests before and after the treatment. These tests included hematology (hemoglobin, WBC, platelets), electrolytes (sodium, potassium, calcium), kidney function (creatinine), liver function (bilirubin, alkaline phosphatase, SGOT, SGPT, LDH), Ig profile, complement, blood culture and Factor VIII/IX levels. No significant changes were noted in the hematology, chemistry and kidney or liver function parameters. Albumin removal was found to vary between 2 and 26%. No correlation was observed between depletion number and the extent of removal of albumin.

Table 6. Adverse events observed during U.S. Hemophilia study with the Excorim® Immunoadsorption System during 87 depletion procedures for 22 patients.

Adverse Event	Number of Patients	Percentage of Patients	Number of Events	Frequency
Gastrointestinal				
nausea	2	9	2	2
vomiting	2	9	2	2
severe abdominal pain	1	5	1	1
Neurological				
tingling	3	14	4	5
numbness	2	9	3	3
dizziness	1	5	1	1
Hematological				
Thrombocytopenia	1	5	1	1
Decreased Ionized Calcium	1	5	1	1
Blood culture positive for coagulase negative *Staph.*	1	5	1	1
Cardiovascular				
Hypotension	2	9	3	3
Bradycardia	3	14	5	6
Tachycardia	7	33	13	15
Hypertension	2	9	2	2
Body as a Whole				
Restlessness	1	5	1	1
Flu	1	5	1	1
Oozing from catheter	1	5	1	1
insertion site	1	5	1	1
Chills	1	5	1	1
Shivering	1	5	1	1
Fever	12	57	23	26
Cramping in toes and feet	1	5	1	1

B. Foreign hemophilia studies

In Europe, the Excorim® Immunoadsorption System was evaluated for acute removal of immunoglobulins from patients with clinically significant titers of antibodies against Factor VIII or IX. Twenty nine patients were treated at three sites in Europe. There were 34 evaluable treatments, which included 66 depletion procedures. The mean BU reduction per treatment was 84.3 ± 23.9%. The following adverse events were observed: hematoma in groin area, fever, bleeding, thrombotic heart complications of Factor IX concentrates, inflammatory reaction with hemolysis and fever (attributed to isoagglutinins against blood group A), septicemia and blood access related problems. These reactions were observed in 1 or 2 patients. Adverse events of this type can be observed with any extracorporeal procedure, especially when citrate anticoagulant and adjunctive immunosuppressive or cytotoxic therapy are used.

Follow-up data were available on 22 of the 29 patients. Nineteen of the patients were treated to stop bleeding, of these, 15 responded positively. Three patients were treated prior to surgery and all of these patients responded favorably.

One patient was treated in Canada. Seven plasma volumes were processed over a three day period of the treatment course. A 94% reduction in inhibitor was observed. A second course of treatment showed a 97% reduction in inhibitor. The patient experienced no adverse effects due to the treatment.

C. United States studies for treatment of other diseases

The Excorim® Immunoadsorption System was evaluated in two clinical trials in the United States for the treatment of diseases other than hemophilia. These studies provide supporting evidence for the safety of the system.

1. Alloimmunized patients refractory to platelet transfusions

   This study was performed to determine the feasibility of using the Excorim® Immunoadsorption system to improve the transfusion response of patients refractory to platelet transfusions due to platelet alloimmunization. Three patients were enrolled at one site. Each patient received at least 6, but no more than 8 procedures. The reduction in IgG levels was similar to that observed in the U.S. hemophilia study.

Adverse events included citrate reactions, nausea, anxiety and pain at the blood access site. There were two deaths during the study. In both cases, the deaths were caused by complications of the patient's underlying disease and were not related to the use of the device.

2. Renal transplant patients

This study was performed to evaluate the use of the Excorim® Immunoadsorption system for removal of immunoglobulins from the plasma of patients with End Stage Renal Disease (ESRD) who were candidates for a renal transplant and who were hypersensitized to HLA-type antigens. The study was performed at one site in the United States and 6 sites in Europe. Twenty nine patients with ESRD were studied. Twenty eight patients received one treatment, consisting of an average of 5.2 consecutive depletion procedures. One patient received two treatments. For each depletion procedure, two to three total plasma volumes were processed.

Reductions in immunoglobulins (i.e., IgG, IgA, IgM) and albumin were similar to those observed for the U.S. hemophilia study.

Adverse events were recorded for each patient and at each depletion procedure and are given in Table 7 below. All events were classified as mild, transient and easily managed with no procedure having to be discontinued because of the occurrence of an adverse event. Two patients died during the follow-up portion of the study. Both deaths were attributed to the patient's underlying disease condition and were not related to the use of the device. One patient had fever, lower quadrant tenderness and elevated liver enzymes during the treatment. Probable non-A, non-B hepatitis related to blood transfusion was diagnosed.

Table 7. Adverse events experienced by patients in U.S. ESRD Study with the Excorim® Immunoadsorption System

	No. of Events (Frequency %)	*No. of Patients*
Nausea and Vomiting	3 (7)	3
Cardiovascular:		
Shortness of breath	4 (9)	3
Hypotension	10 (22)	5
Hypertension	1 (2)	1
Fever	5 (11)	3
Shivering/Chills	11 (24)	5
Citrate Toxicity:		
Numbness/Tingling	17 (37)	8
Cramps	4 (9)	4

All patients were monitored during treatment and follow-up for a variety of hematological, blood chemistries and serological parameters. All values remained within normal limits except for minor changes in hemoglobin, WBC, platelets, serum potassium and albumin. None of these changes were considered by the investigator to be clinically significant.

D. Foreign studies for treatment of other diseases

Additional studies have been conducted with the Excorim® Immunoadsorption system in Europe and Canada for the treatment of a variety of immunological diseases. Fifteen patients were studied in uncontrolled trials. The percent reduction in IgG, IgA, IgM and albumin were similar to those observed in the U.S. studies discussed above. The adverse events were primarily related to citrate reactions and were similar in severity to those observed during the U.S. clinical studies. One patient death occurred, however, the death was attributed to the patient's underlying disease state and was not related to the use of the device.

The Excorim® Immunoadsorption system was evaluated in a randomized, controlled trial in Sweden where the control patients received plasmapheresis. Patients were enrolled with a variety of immunological diseases. Forty two patients were enrolled in the Excorim® arm and 43 patients were enrolled in the control arm. The adverse events experienced by patients receiving the Excorim® treatment were not significantly different from those experienced by patients in the control arm. Four deaths occurred (1 in the Excorim® arm and 3 in the plasmapheresis arm). These deaths were attributed to the patient's underlying disease state and were not related to the use of the device. One depletion procedure was discontinued due to excessive administration of citrate. The pH alarm on the Citem® 10 monitor alerted the operator and appropriate action was taken.

E. Data from the Published Literature

Numerous articles have been published that discuss the treatment of patients in Europe and Canada with the Excorim® Immunoadsorption system for a variety of immunological diseases[7-28]. These articles describe the treatment of over 200 patients. The mean percent reduction in IgG reported ranged from 71 to 97% and was similar to the values observed during the U.S. clinical studies. Reported side effects included numbness and tingling, hypotension, shivering, fever, leukopenia, hypocalcemia and paresthesia. One case of treatment discontinuation was reported in which a patient experienced fever and leukopenia (< 3000 WBC). Four deaths

were reported in the published papers, however, no relationship was found between the deaths and treatment with the device.

X. CONCLUSIONS DRAWN FROM PRE-CLINICAL AND CLINICAL STUDIES

The pre-clinical safety and performance studies demonstrate that the design of the Excorim® Immunoadsorption system is appropriate for this intended use when operated by knowledgeable, trained personnel. The pre-clinical performance studies indicate that the Immunosorba® columns, when used in conjunction with the Citem® 10 monitor, will remove over 90% of the IgG from circulating plasma with a high degree of specificity. Biocompatibility and toxicological testing of the Protein A-Sepharose® adsorbent, the column housing materials, and the Excorim® medical lines indicate that these materials are safe for this intended use. Electrical safety and software test results demonstrate that the Citem® 10 monitor can be used safely when operated by trained personnel.

The limited clinical data presented are not adequate to definitively establish the safety and effectiveness of the device for the treatment of hemophilia patients with Factor VIII or IX inhibitor levels above 10 BU/ml. However, the data demonstrate that the device does remove large amounts of IgG, which can be of significant benefit to hemophilia patients who are currently undergoing a bleeding episode or who wish to prepare for elective surgery. The adverse events experienced with the use of this device are mild and are similar to those experienced for other extracorporeal procedures. Data obtained from the treatment of patients with other disease conditions support the conclusion that the frequency of adverse events experienced with this device is low, and the events are generally transient and readily resolved.

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, and that the probable benefit to health from using the device outweighs the risk of injury or illness, especially considering the probable risks and benefits of currently available devices or alternative forms of treatment for this disease.

XI. PANEL RECOMMENDATIONS

The Gastroenterology/Urology panel did not specifically consider this HDE application. However, on July 29, 1986, they did review a premarket approval application (PMA) for a similar product, the IMRE Prosorba® column for the treatment of patients with idiopathic thrombocytopenic purpura having platelet numbers less than 100,000/mm^3. During their review, the panel raised concerns regarding the potential toxicity of Protein A, potential leaching of Protein A and

particulates from the column and sterility of the adsorbent. The sponsor of this HDE has provided adequate test data to demonstrate the safety of the Protein A adsorbent with regard to toxicity, leaching and sterility. The panel also recommended that all users of the IMRE Prosorba® column undergo a detailed training program. As a condition of approval for this device, all users of the Excorim® Immunoadsorption system will also be required to undergo a training program.

XII. CDRH DECISION

CDRH has determined that, based on the data submitted in this HDE application, the Excorim® Immunoadsorption system will not expose patients to an unreasonable risk or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval order on APR 6 1998.

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See the Professional Labeling (Attachment 1)

Warnings, Hazards to Health with the Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Effects in the Labeling

Information for the Patient: See Patient Labeling (Attachment 2)

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DRAFT

Important Information for the Excorim® Immunoadsorption System

HUMANITARIAN DEVICE. Authorized by United States Law for use in the treatment of patients with hemophilia A or B and inhibitor levels above 10 BU/mL. The effectiveness of this device for this use has not been demonstrated.

CAUTION: Federal law restricts this device to sale, distribution and use by or on the order of a physician with appropriate training and experience.

DEVICE DESCRIPTION

The Excorim® Immunoadsorption System consists of the following components:

- **Immunosorba® Protein A Column**

  The Immunosorba column contains Protein A covalently immobilized to a Sepharose® support matrix. Each column contains 62.5 mL of Protein A Sepharose® adsorbent, capable of binding 1.2 g of immunoglobulin. Each treatment uses two columns.

- **Citem 10® Monitor plus accessories**

  The Citem 10® Monitor is designed to monitor and control treatments. The Citem 10® Monitor is used to control flow of fluids through the Immunosorba® Protein A Column.

- **Excorim® Medical Lines (including inlet line, outlet line, COBE® Spectra™ connection lines, waste bag, double bag, and fraction bag)**

  The medical lines are designed specifically for use with the Excorim® Immunoadsorption System. The medical lines are sterile, disposable and for single use only.

- **Disposable pH-electrode**

  The pH-electrode monitors the pH of the fluid returned to the patient. The electrode is sterile, disposable and for single use only.

- **Buffer PA and Eluant PA solutions**

  Buffer PA and Eluant PA are sterile packaged solutions for flushing and regeneration of the Immunosorba® Protein A Column.

- **Thimerosal 10% solution**

  The thimerosal solution is a sterile 10% solution of merthiolate. The thimerosal solution is diluted with one liter of Buffer PA and is used to preserve the Immunosorba columns between procedures.

DEVICE OPERATION

The Excorim® Immunoadsorption System is designed to continuously remove immunoglobulin molecules from the plasma of hemophilia patients. To use the device, the patient's plasma is separated from the blood with the COBE® Spectra™ Apheresis System. After treatment of the patient's plasma with the Excorim® Immunoadsorption System, the plasma is sent back to the COBE® Spectra™ system for return to the patient. The Excorim® Immunoadsorption System automatically cycles the plasma between two Immunosorba® Protein A Columns. While one column is removing immunoglobulins, the other column is being regenerated. At the end of the procedure, the system flushes both columns, returns the plasma to the COBE® Spectra™ system, and preserves the columns with a 0.1% thimerosal solution. The columns are then stored at 2° to 8°C for use by the same patient at the next immunoadsorption procedure.

INDICATIONS FOR USE

The Excorim® Immunoadsorption System is indicated for use in the treatment of patients with hemophilia A and B who have Factor VIII or Factor IX inhibitor titers above 10 Bethesda Units/mL (BU/mL). The purpose of the system is to lower the inhibitor levels so that routine clotting factor replacement therapy can be considered. It may be used in an acute setting (to control bleeding during an acute hemorrhage or for emergency surgery) or as a preventative measure to prepare patients for elective surgery.

CONTRAINDICATIONS

The Excorim® Immunoadsorption System is contraindicated for the following conditions:

- Patients for whom adequate anticoagulation with acid citrate dextrose (ACD) either alone or in combination with heparin, cannot be maintained.
- Patients who are receiving angiotensin converting enzyme (ACE) inhibitors.
- Patients with cardiovascular and/or pulmonary disease of such a degree that extracorporeal therapy is not permissible.
- Patients with a sepsis.
- Patients with a known allergy to Protein A or Staphylococcus-derived products.
- Patients with a known allergy or sensitivity to thimerosal (merthiolate).

WARNINGS

General

1. **The Excorim® Immunoadsorption System should only be used by qualified health care professionals who have completed the required training program.** Carefully read the Excorim® Immunoadsorption System Operator's Manual and the instructions for use for the Immunosorba® Protein A Columns, Citem 10® Monitor, medical lines or other accompanying device before operating the Excorim® Immunoadsorption System. Before the first use, ensure that the installation test has been successfully performed.

2. Operate this device only in accordance with the procedures contained in the Excorim® Immunoadsorption System Operator's Manual and the instructions for use. **The use of operating procedures other than those published by the manufacturer or the use of accessory devices not recommended by the manufacturer can result in patient injury or death.**

3. The Excorim® Immunoadsorption System is contraindicated for patients with sepsis. Adequate preservation of the Immunosorba® Protein A Columns between depletion procedures cannot be guaranteed for patients with sepsis.

Device Set-up

4. Before treatment begins, make sure that the preserving agent is thoroughly rinsed out of both columns, as described in the Excorim® Immunoadsorption System Operator's Manual. **If the preserving agent (0.1% Thimerosal) is not properly rinsed from the columns, serious patient injury or death may occur**. During the rinse out of the columns (i.e. during Prepare), check that the pumps are functioning, fluid is passing through each of the columns, and the fluid is passing to the waste bag.

5. Use only medical lines, bags, columns, and pH-electrodes manufactured by Excorim for the Citem 10® Monitor and only COBE tubing sets for the COBE® Spectra™ Apheresis System. **The use of non-Excorim® Medical Lines or non-COBE tubing sets can result in patient injury or death.**

6. Make sure that the Immunosorba® Protein A Columns are clearly and correctly labeled with patient identification data before treatment and verify that the correct column is used prior to each procedure. Prior to each procedure insure that the columns are within their expiration date. **Serious injury or death may occur if the column is used for the wrong patient or is used past the expiration date.**

7. The sterilized medical lines are designed for single use; **do not resterilize or reuse**.

8. Do not bring into contact any chemicals or solvents with the exterior of any medical line, connection, or column.

9. Do not use any medical line, connection, or column if the packaging has been opened or damaged, or the unit itself appears to be damaged.

10. It is the responsibility of the operator to calibrate the detectors as described in the Excorim® Immunoadsorption System Operator's Manual.

11. Prior to the use of any solutions check that the container is not damaged and that the solution is clear.

12. When handling the medical lines, columns, or solutions, hospital and clinic personnel should take adequate precautions at all time to prevent exposure to or the transmission of the hepatitis virus, human immunodeficiency virus (HIV), or other infectious agents.

Treatment Phase

13. At the end of treatment, all connections to the patient must be disconnected before preservation fluid is supplied to the columns. **Serious patient injury or death may occur if the patient comes into contact with the preservation fluid (0.1% Thimerosal).**

14. Do not connect the patient to the Citem 10® Monitor during any service or maintenance procedure. **Serious injury or death may result.**

15. Use only Buffer PA, Eluant PA and Thimerosal 10% solutions that are supplied with the Excorim® Immunoadsorption System. **Use of other solutions can result in patient injury or death.**

16. All blood and fluid flow paths of the medical lines, bags, fluids, and pH-electrodes are sterile and nonpyrogenic. Use aseptic technique when handling the blood and fluid lines.

17. The Citem 10® Monitor does not have an air bubble detection system to protect the patient from air embolism. The COBE® Spectra™ Apheresis System device includes air embolism protection; therefore, it is required that the Excorim® Immunoadsorption System only be used with the COBE® Spectra™ Apheresis System.

Device Shut-down

18. The thimerosal solution is not for direct intravenous injection/infusion.

19. Before using, check that the vial of thimerosal is not damaged and that the solution is clear.

20. The 0.1% thimerosal solution is a preservative (and not a disinfectant). Care should be taken to keep the columns from becoming contaminated between depletion procedures.

21. There are no user-serviceable components in the Citem 10® Monitor. Trained and qualified service technicians must perform all service repairs.

22. Do not freeze the columns.

PRECAUTIONS

General

1. The safety of the Excorim® Immunoadsorption System has not been established for: (1) pregnant women, (2) patients less than 40 kg in body weight, and (3) patients less than 12 years of age.

2. Care should be taken to operate the COBE® Spectra™ Apheresis System properly. If platelets are allowed to spill over, or if an insufficient amount of citrate is used, column performance will suffer.

3. Removal rates for IgG, IgM, IgA, and IgE will vary from patient to patient. Each patient should be carefully monitored before and after each depletion procedure.

4. The Immunosorba® Protein A Columns can be used multiple times for one individual patient. A column that displays a low Column Performance Index (CPI) (i.e., has a CPI less than 20) is inefficient and should be replaced. Refer to Operator's Manual for details.

5. During the clinical evaluation of the device, there were several patients with very high inhibitor levels for whom multiple procedures failed to reduce inhibitor levels below 10 BU/mL. Therefore, there is a risk that treatment with this device may not produce the desired outcome (i.e., lowering of inhibitor levels below 10 BU/mL). If this occurs, there is a theoretical risk of uncontrollable bleeding at the blood access sites if hemostasis cannot be achieved.

6. In addition to removal of IgG, the Immunosorba® Protein A Column also removes lesser amounts of IgA, IgM, and IgE. Although no adverse effects were noted in the clinical evaluation of the device due to depletion of these factors, there is a theoretical risk of infection due to immune suppression.

Citem 10® Monitor

7. When exposed to excessive electromagnetic disturbance, such as electrostatic discharge, the Citem 10® Monitor reacts by entering a patient safe state, i.e. all pumps stop and a

power failure alarm is generated. The monitor will resume its operation when the electromagnetic disturbance has disappeared and the operator initiates a restart after power failure alarm (see page 4 - 12 of the Excorim® Immunoadsorption System Operator's Manual for a complete description of the Power Failure Alarm).

8. To protect the Citem 10® Monitor from excessive electromagnetic fields, make sure that mobile telephones (and other similar devices) are not used in the vicinity of the monitor while in operation.

9. Avoid spilling fluids on the monitor as this may effect the functioning of detectors, valves, etc. If spillage occurs, clean immediately with a soft cloth moistened with a mild cleaning agent. Do not use iodine-based disinfection or cleaning agents as these substances can damage some of the plastic materials.

10. Avoid placing the monitor in direct sunlight or directing bright lamps onto the detectors. Bright light on the optical detectors, may cause incorrect readings.

11. The UV lamp in the monitor requires about 15 minutes to warm up before the optical detectors can be calibrated.

12. The pump covers must be closed when the pumps are running.

13. In the event of a Citem 10® Monitor technical failure, the operator is required to manually elute and fill the columns with preservative.

14. Do not block the ventilation slots on the back of the monitor.

15. All electrical installations must comply with all applicable local electrical codes and the manufacturer's specification.

pH detector

16. The pH detector may be sensitive to electrical disturbances caused by other medical devices, for example, ECG monitors and/or defibrillators. Always disconnect the lines between the patient and the monitors (including plasma separation equipment) before using any other electrically-powered medical device on the patient.

17. To prevent plasma from leaking through the pH chamber, DO NOT place clamps on the lines above the pH detector when the pumps are operating. Plasma or other residue can block the aperture of the detectors causing inaccurate fluid sorting.

18. The pH-electrode must be handled with great care and instructions must be followed carefully.

Solutions and Medical Lines

19. Before use, the 10% thimerosal concentrate should be made into a 0.1% solution. Thimerosal is harmful if swallowed or comes in contact with skin. There is a risk of cumulative effects. Users should wear protective gloves, and if thimerosal comes into contact with the skin, rinse immediately with water.

20. Keep Buffer PA and Eluant PA at room temperature during the procedure.

21. Check that all medical lines have been installed in the correct positions and that they are not kinked. Make sure that all lines passing through valves are on the correct side of the valve and that all the pump segments are placed in the correct pumps. Use the printed diagram on the front panel as a guide.

ADVERSE EVENTS

The adverse effects that were observed during clinical evaluation of the Excorim® Immunoadsorption System include transient episodes of nausea and vomiting, fever, chills, numbness, tingling, paresthesia, pain, cramps, headache, dyspnea, tremor, dizziness and changes in blood pressure and heart rate. These effects have been observed with other extracorporeal procedures, especially when citrate anticoagulant and immunosuppressive or cytotoxic drugs are used concomitantly.

Other potential complications which were not seen during clinical evaluation include blood or plasma loss from leaks, bleeding or clotting from improper anticoagulant use, and fluid balance mismanagement.

In addition to removal of IgG, the column also removes lesser amounts of IgA, IgM, IgE and albumin. Although no adverse effects were noted due to depletion of these factors, there is a theoretical risk of infection due to immune suppression.

During the clinical evaluation of the device, there were several patients with very high inhibitor levels for whom multiple procedures failed to reduce inhibitor levels below 10 BU/mL. Therefore, there is a risk that treatment with this device may not produce the desired outcome (i.e., lowering of inhibitor levels below 10 BU/mL). If this occurs, there is a theoretical risk of uncontrollable bleeding at the blood access sites if hemostasis cannot be achieved.

UNITED STATES CLINICAL EXPERIENCE

A study was performed to evaluate the acute removal of immunoglobulins from the plasma of hemophilia patients in whom clinically significant titers of antibodies against Factor VIII or IX had been demonstrated.

The study was performed at 13 sites in the United States. Twenty-two patients were enrolled. Of these 22 patients, there were 19 males and 3 females, and the average age was 44. Thirteen patients had congenital hemophilia and 9 had acquired hemophilia. Nineteen patients had Factor VIII deficiency, 1 had Factor IX deficiency, and 2 had other coagulation disorders. The study had the following inclusion/exclusion criteria:

Inclusion criteria

- Patient's inhibitor level exceeded 10 BU/mL
- Patient had a documented anamnestic response
- Patient presented with one of the following: (1) Acute bleeding (2) Need for surgery (3) Recurrent, disabling bleeding.

Exclusion Criteria

- Pregnancy
- Active bacterial infection
- Active hepatitis or Acquired Immunodeficiency Syndrome (AIDS)
- Patient unable to give informed consent
- Age over 70
- Weight under 40 kg

Deviations from Protocol

Four of the 22 patients had inhibitor levels less than 10 BU/mL upon enrollment. Two patients were over 70 years of age, one patient's weight was under 40 kg and one patient had active hepatitis or AIDS.

Treatment Schedule

Each treatment consisted of a series of individual depletion procedures that were performed consecutively. A total of 22 patients were evaluated which constituted 25 treatments, and 87 depletion procedures. Typically 3.1 plasma volumes were processed for each depletion procedure and each treatment consisted of 3.5 depletion procedures. The mean number of plasma volumes treated over the entire treatment was 10.2.

The reason for enrollment is available for 23 of the 25 treatments. Of these 23 treatments, 13 were for patients experiencing acute bleeding. Seven of these 13 treatments were for patients who were also described as being disabled by recurring bleeding. An additional 6 treatments were provided to patients described only as disabled by recurring bleeding. Four treatments were provided to patients who required unavoidable surgery.

Effectiveness Evaluations

For the 22 patients, the mean percent reduction in IgG, Bethesda Unit (BU), IgM, IgE, IgA and albumin are shown in Table 1. Only the 20 patients with Factor VIII and IX inhibitors are included in the results for Bethesda Unit.

Table 1. Mean Percent Reduction observed over entire treatment course in U.S. Hemophilia Study.

	Mean Percent Reduction	Standard Deviation	Number of Treatments*	No. of Patients†
BU	81.0	19.7	19	18
IgG	76.2	23.2	24	21
IgM	50.7	26.1	23	20
IgE	42.0	48.7	8	8
IgA	39.2	18.2	23	20
Albumin	22.8	11.0	14	13

*Number of treatments for which data are available †Number of patients for which data are available.

The 25 treatments consisted of from 1 to 7 depletion procedures. As shown in Tables 2-3, the mean pre-treatment values for IgG and BU show a declining trend from the first depletion procedure. Regardless of the initial concentration, the Excorim® Immunoadsorption System was found to lower IgG by approximately the same mean percent change for each depletion procedure.

Table 2. Reduction in IgG observed per depletion procedure during U.S. Hemophilia study with Excorim® Immunoadsorption System.

Depletion Procedure No.	*No. of Patients‡*	*No. of Treatments†*	*Pre (mg/mL) Mean ± SD (N)*	*Post (mg/mL) Mean ± SD (N)*	*Mean Percent Change*
1	22	25	13.39 ± 8.10 (25)	5.12 ± 4.99 (24)	67.9 ± 16.8 (24)
2	21	24	8.04 ± 5.69 (24)	3.60 ± 3.22 (22)	59.5 ± 22.3 (22)
3	16	16	6.82 ± 3.75 (16)	3.05 ± 2.93 (15)	59.9 ± 19.2 (15)
4	10	10	6.59 ± 4.29 (10)	2.70 ± 2.37 (9)	63.4 ± 16.3 (9)
5	7	7	7.56 ± 5.32 (6)	2.54 ± 2.36 (7)	66.5 ± 9.2 (6)
6	4	4	2.82 ± 1.12 (3)	1.06 ± 0.54 (4)	56.9 ± 29.2 (3)
7	1	1	5.40 (1)	n/a*	n/a*

*Values not measured †Number of treatments for which data are available ‡Number of patients for which data are available

Table 3. Reduction in BU observed per depletion procedure during U.S. Hemophilia study with Excorim® Immunoadsorption System.

Depletion Procedure No.	*No. of Patients‡*	*No. of Treatments†*	*Pre (BU/mL) Mean ± SD (N)*	*Post (BU/mL) Mean ± SD (N)*	*Mean Percent Change*
1	20	22	882 ± 2848 (21)	93 ± 186 (22)	66 ± 25 (21)
2	19	21	401 ± 1167 (21)	97 ± 257 (21)	69 ± 23 (21)
3	15	15	230 ± 466 (15)	132 ± 383 (15)	69 ± 23 (15)
4	9	9	431 ± 941 (9)	23 ± 32 (8)	75 ± 20 (8)
5	7	7	562 ± 1055 (6)	129 ± 237 (6)	79 ± 9 (6)
6	4	4	452 ± 489 (3)	235 ± 410 (4)	69 ± 29 (3)
7	1	1	2200 (1)	n/a*	n/a*

*Values not measured †Number of treatments for which data are available ‡Number of patients for which data are available

As shown in Table 4 below, follow-up data on clinical outcomes is available on 13 of the 22 patients.

Table 4. Follow-up data on clinical outcomes for U.S. Hemophilia study with Excorim® Immunoadsorption System.

Patient Number	Presented to stop bleeding	Presented to establish factor level prior to surgery	Presented to induce immune tolerance	BU lowered to less than 10/mL	Therapeutic level of factor achieved	Bleeding stopped or surgery successful	Bleeding not resolved
1	X	X		X	X	X	
2			X	X	X		
3	X			X	X		
4	X			*			
5		X	X	X			
6	X						
7	X			X			
8		X		X	X	X	
9	X			X			
10	X						
11	X					X	
12	X						
13	X					X	
14	X						
15	X			X			
16	X			X		X	
17	X			X			X
18	X						X
19	X					X	
20	X			*		X	
21	X			X		X	
22		X		X		X	
Total	18	4	2	12	4	9	2

*Patient with other coagulation disorders, not measurable by Bethesda Units.

The investigators reported that bleeding was stopped or surgery was successful in nine of the 13 patients for which follow-up data was available. Bleeding was not resolved for two patients. For another two patients, therapeutic levels of coagulation factor were achieved, however, no information is available on whether bleeding was stopped or surgery was successful.

Safety Evaluations

There were six deaths reported by physicians conducting this study. The causes of death are listed below. None of the deaths were attributed to the use of the device.

1. Patient's death was attributable to the development of pneumonia as a consequence of chronic lymphocytic leukemia.
2. Patient's death was attributable to congestive heart failure.
3. Patient's death was due to a seizure as a result of meperidine administration for analgesia.
4. Patient's death was attributable to acute internal bleeding.
5. Patient's death was due to a massive hemothorax and respiratory distress due both to the collapse of the right lung and focal interstitial pneumonitis.
6. Patient had multiple contributory causes to his death which included upper & lower gastrointestinal bleeding, *Staphylococcus* sepsis, middle lobe pneumonia, disseminated intravascular coagulation, and intracranial hemorrhage.

The adverse events observed during the study are shown in Table 5.

Table 5. Adverse events observed during U.S. Hemophilia study with the Excorim® Immunoadsorption System during 87 depletion procedures for 22 patients.

Adverse Event	Number of Patients	Percentage of Patients	Number of Events	Frequency
Gastrointestinal				
nausea	2	9	2	2
vomiting	2	9	2	2
severe abdominal pain	1	5	1	1
Neurological				
tingling	3	14	4	5
numbness	2	9	3	3
dizziness	1	5	1	1
Hematological				
Thrombocytopenia	1	5	1	1
Decreased Ionized Calcium	1	5	1	1
Blood culture positive for coagulase negative *Staph.*	1	5	1	1
Cardiovascular				
Hypotension	2	9	3	3
Bradycardia	3	14	5	6
Tachycardia	7	33	13	15
Hypertension	2	9	2	2
Body as a Whole				
Restlessness	1	5	1	1
Flu	1	5	1	1
Oozing from catheter	1	5	1	1
insertion site	1	5	1	1
Chills	1	5	1	1
Shivering	1	5	1	1
Fever	12	57	23	26
Cramping in toes and feet	1	5	1	1

Many of these reported adverse events can be experienced by patients during any extracorporeal procedure. No depletion procedure was discontinued prematurely due to any of these adverse events. In addition to these adverse events that were observed during the depletion procedures, the following adverse events were reported during follow-up visits: nausea (1), tingling (1), light-headedness (1), thrombocytopenia (2), oozing from venous catheter insertion site (1).

No infectious complications were attributed to the procedure, although one patient had a positive blood culture for coagulase negative *Staphylococcus*. The patient later died of multiple causes.

Albumin removal was found to vary between 2 and 26%. No correlation was observed between depletion number and the extent of removal of albumin. All patients enrolled in the study were

subjected to a panel of standard laboratory tests before and after the treatment. These tests included hematology (hemoglobin, WBC, platelets), electrolytes (sodium, potassium, calcium), kidney function (creatinine), liver function (bilirubin, alkaline phosphatase, SGOT, SGPT, LDH), Ig profile, complement, blood culture and Factor VIII/IX levels. No significant changes were noted in the hematology, chemistry, kidney or liver function parameters.

CLINICAL EXPERIENCE IN EUROPE AND CANADA

In Europe, the Excorim® Immunoadsorption System was evaluated for acute removal of immunoglobulins from patients with clinically significant titers of antibodies against Factor VIII or IX. Twenty nine patients were treated at three sites in Europe. There were 34 evaluable treatments, which included 66 depletion procedures. The mean BU reduction per treatment was 84.3 ± 23.9%. The following adverse events were observed: hematoma in groin area, fever, bleeding, thrombotic heart complications of Factor IX concentrates, inflammatory reaction with hemolysis and fever (attributed to isoagglutinins against blood group A), septicemia and blood access related problems. These reactions were observed in 1 or 2 patients. Reactions of this type can be observed with any extracorporeal procedure, especially when citrate anticoagulant and adjunctive immunosuppressive or cytotoxic therapy are used. Follow-up data was available on 22 of the 29 patients. Nineteen of the patients were treated to stop bleeding, of these, 15 responded positively. Three patients were treated prior to surgery and all of these patients responded favorably.

One patient was treated in Canada. Seven plasma volumes were processed over a three day period of the treatment course. A 94% reduction in inhibitor was observed. A second course of treatment showed a 97% reduction in inhibitor. The patient experienced no adverse effects due to the treatment.

U.S. AND WORLDWIDE EXPERIENCE FOR THE TREATMENT OF OTHER DISEASES

The Excorim® Immunoadsorption System has been investigated in the U.S. and other foreign countries for treatment of a variety of immunological diseases. The removal of IgG, IgA, IgM and albumin was found to be similar to that observed in the hemophilia studies. Adverse events were also similar in frequency and severity to those already observed.

CLINICIAN USE INFORMATION

Operator training

All users of the Excorim® Immunoadsorption System are required to undergo a training program prior to use of the device.

Directions for Use

The extent of inhibitor reduction in the patient's plasma will be influenced by several factors: the number of depletion procedures, the amount of plasma treated during each procedure, re-equilibration of inhibitors from the extravascular space, and the patient's rate of synthesis.

The general course of treatment is as follows: The Excorim® Immunoadsorption System is used to treat three (3) plasma volumes which reduces the patient's inhibitor titer. The titer will then rise due to re-equilibration of IgG from the extravascular space and the patient's rate of synthesis. It is recommended that inhibitor levels be measured before and after each depletion procedure and that depletion procedures be continued on a daily basis until the inhibitors have been reduced to the desired level. Treating more than 3 plasma volumes will remove more inhibitors but the efficiency will be reduced as the plasma inhibitor concentration is decreasing. Treating the following day will allow time for re-equilibration with the extravascular space resulting in an improved efficiency of inhibitor removal. The volume of plasma treated each day and the number of treatment days will depend upon the patients' initial inhibitor level and the urgency of starting factor replacement. Monitoring of inhibitor levels will aid in making these determinations.

It is recommended that only after achieving the desired titer should factor replacement therapy be started. Patient exposure to factor (and possibly other products that contain trace quantities of factor) will initiate the start of an immunologic response leading to an anamnestic rise in inhibitor level approximately 5 days following the exposure. Therefore, to maximize the period of hemostasis, it is recommended to not give factor until the titer has been reduced to the desired level. Factor replacement therapy should be sufficient to neutralize the circulating inhibitors (accounting for re-equilibration with the extravascular space) and to achieve the desired plasma level for hemostasis. Factor replacement therapy should be continued until the anamnestic response cannot be overcome.

Therapy with the Excorim® Immunoadsorption System does not produce sustained lowering of the inhibitor titers. Following an immunoadsorption procedure the titer will increase due to re-equilibration of inhibitor from the extravascular space, as well as from any new synthesis of inhibitor which may occur. Following initiation of the factor replacement therapy the patient's anamnestic response will probably cause the titer to eventually become higher than the pre treatment titer. Careful monitoring of each patient's clinical condition throughout the treatment course is recommended. Please refer to the Operator's Manual for detailed instructions on how to use the system.

Human clinical trials conducted in the United States have included treatments of up to seven (7) depletion procedures. Patients enrolled into these studies had a mean of three (3) plasma volumes and a maximum of eight (8) plasma volumes treated per procedure (a maximum of 40 plasma volumes for the treatment course).

Currently the Immunosorba® Protein A Columns have a 12 month expiration date from the time of manufacturing. Make sure that the Immunosorba® Protein A Columns are clearly and correctly labeled with patient identification data before treatment and verify that the correct column is used prior to each procedure.

Refer to the Warnings and Precautions listed above for proper use of the device.

PATIENT INFORMATION

All patients should receive the patient information sheet, titled "Treatment with the Excorim® Immunoadsorption System: Information for the Patient" prior to initiating treatment.

COMPLAINTS RELATED TO THE EXCORIM® IMMUNOADSORPTION SYSTEM

Complaints can be submitted by telephone followed by a written complaint report to the local retailer, or directly to COBE at:

COBE BCT®
1201 Oak Street
Lakewood, Colorado 80215-4498

Telephone: 1-800-COBE-BCT or 1-303-232-6800

Complaints related to injury, death or any safety hazard should be submitted immediately.

The following must be covered in the complaint report:

Name of the hospital
Name and telephone number of the key contact at the hospital
Complaint description
Incident date
What medical intervention took place
Citem 10® Monitor serial number
COBE® Spectra™ Apheresis System serial number
Lot numbers of the Immunosorba® Protein A Columns
Lot number of the pH-electrode
Lot numbers of all medical lines
Lot numbers of all solutions

Treatment with the Excorim® Immunoadsorption System:
Information for the Patient

HUMANITARIAN DEVICE. Authorized by United States Law for use in the treatment of patients with hemophilia A or B and inhibitor levels above 10 BU/mL. The effectiveness of this device for this use has not been demonstrated.

General Information and Procedures

The Excorim® Immunoadsorption System is intended for use in hemophilia patients with inhibitors to Factor VIII or Factor IX. The inhibitors can react with Factor VIII and IX making factor addition ineffective. The function of the system is to reduce the inhibitors to these factors so that normal clotting factor replacement therapy can be used. Because the inhibitors have been reduced, factor replacement therapy may be effective in controlling bleeding or permitting surgery.

If you choose to undergo this procedure, blood will be removed from one of your blood vessels, treated, and then returned to your body. The treatment process uses two devices. In the first device, the plasma (liquid) portion of the blood will be separated from the blood cells. In the second device, your plasma will pass through an adsorption column. As the plasma goes through this column, inhibitors and antibodies will stick to the column. Your treated plasma will be re-mixed with the blood cells and will be returned to you. This procedure is a continuous process which can take from 2 to 9 hours. Procedures will be conducted once per day for 1 to 7 days. The length and frequency of therapy will be dependent on the severity of your condition and your particular needs.

Inhibitors can react with Factor VIII and IX thus making the factor ineffective. Therefore, removal of these inhibitors will allow your doctor to give you Factor VIII and IX and thus help stop bleeding or prepare for surgery.

Possible Benefits and Risks of Undergoing this Procedure

The potential benefit of undergoing this procedure is the reduction in inhibitors that would react to the clotting factor given to you that will help to control bleeding or could allow for surgery.

The possible risks include:

* Numbness and tingling from the use of citrate (a product used to keep the blood from clotting in the machine).
* Nausea and vomiting.
* Hypotension.

All of the above reactions could occur immediately after your blood has started to be returned to you. These reactions have occurred frequently as a result of having the procedure and/or the use of citrate. The physician may treat these reactions by changing

the speed at which the blood is removed from your body and/or by giving calcium (Tums®).

* Fever has occurred frequently and at various times throughout the procedure. If necessary your fever could be treated with Tylenol®.
* Bleeding at the blood access sites.
* Pain and or discomfort at the blood access sites.

In addition there are other theoretical risks associated with this procedure which include:

* Exposure to foreign particles that are a part of the immunosorbent column that may cause an allergic reaction.
* Susceptibility to infections due to the reduction in antibodies.

You may develop side effects that are unforeseeable at this time in addition to those listed above.

Alternative Therapies

Alternative therapies exist for patients with high levels of inhibitors to Factor VIII and IX, however, they have not been reliable. For patients with inhibitors to Factor VIII and IX, the only predictable mechanism for hemostasis is to achieve circulating levels of these clotting factors. Other forms of therapy which have been used to achieve adequate levels of clotting factor include:

* Exchange of the liquid portion of the blood "Plasmapheresis".
* Use of prothrombin complex concentrates.
* Porcine Factor VIII.

These alternative therapies along with their risks and benefits will be discussed with you.