Cypress Bioscience, Inc.
Prosorba® column

ESSENTIAL PRESCRIBING INFORMATION

Numbers in parentheses ( ) refer to sections in the main part of the product labeling

Device Description: The Prosorba® column employs approximately 200 mg of protein A covalently bound to an inert silica matrix that is contained within a 300 ml polycarbonate housing. Each column contains 123 ± 2 grams of this matrix. Protein A is a component of certain strains of the *Staphylococcus* bacterium and it binds immunoglobulin G (IgG) and IgG bound to an antigen, i.e., circulating immune complex.

Contraindication: The use of this device is contraindicated in patients currently receiving angiotensin converting enzyme (ACE) inhibitor medications due to the incompatibility of these products with many procedures involving apheresis. A minimum 72-hour withdrawal period is recommended prior to administration of the Prosorba® column treatment. See the CONTRAINDICATIONS below and in Section 3 for more information.

Warning: The use of central venous catheters in RA patients was associated with a > 40% rate of infection and/or local clotting. They should only be used with great caution. See WARNINGS below and Section 7 for more information.

Intended Use/Indications:

- The Prosorba® column is indicated for use in the therapeutic removal of immunoglobulin G (IgG) and IgG-containing circulating immune complexes from plasma in patients with idiopathic thrombocytopenic purpura (ITP) having platelet counts less than 100,000mm^3.
- The Prosorba® column is indicated for use in the therapeutic reduction of the signs and symptoms of moderate to severe rheumatoid arthritis in adult patients with long standing disease who have failed or are intolerant to disease-modifying anti-rheumatic drugs (DMARDS). (See Section 2)

Individualization of Treatment: The Prosorba® column should be used with caution under the following circumstances:

- In patients who have underlying or pre-existing conditions which may be exacerbated by apheresis procedures.
- (FOR ITP PATIENTS ONLY) In patients where other concurrent treatments for ITP are being administered.
- (FOR ITP PATIENTS ONLY) In patients with greater than 100,000 platelets/mm^3. Such patients have not been clinically evaluated using Prosorba® column therapy.

Contraindications: The use of this device is contraindicated in patients who:

- Are currently receiving angiotensin-converting-enzyme (ACE) inhibitor medications. ACE-inhibitors represent a potentially life-threatening risk to patients receiving treatment requiring extracorporeal blood procedures. (See NOTE in Section 3)
- Cannot tolerate therapeutic apheresis procedures and have demonstrated a prior hypersensitivity associated with therapeutic apheresis.
- Exhibit evidence of, or have a history of, hypercoagulability.
- Have pre-existing abnormalities of the coagulation system in which activation of the coagulation system may precipitate a thrombotic event or a recent history of thromboembolic events. (See Section 3)

Warnings and Precautions:

- Warning: The Prosorba® column should be used with caution in patients:
  - with inadequate peripheral venous access who require placement of a central venous catheter (see Section 7);
  - where acute fluid shifts may precipitate congestive heart failure;
  - with impaired renal function where expansion or reduction of plasma volume could be harmful;
  - with clinically significant hypotension or borderline hypotension where a further fall in blood pressure could be harmful;
  - with significant vascular disease where a fall in blood pressure could lead to significant post-obstructive physiologic abnormalities;
  - with established or suspected intracranial disease where minor fluid shifts or pressure changes could exacerbate the underlying central nervous system problem;
  - with severe anemia, i.e., Hct < 27, Hgb < 9 (see Section 4);
  - with systemic infection.
- Warning: Should an adverse reaction occur requiring treatment termination and medical intervention, Prosorba® column therapy should not resume until the adverse reaction has dissipated and the patient has stabilized.
- Warning: (FOR RA PATIENTS) Treatment with this device was associated with a drop in hemoglobin, hematocrit and MCV. Patients should be closely monitored for anemia during treatment and follow-up.
- Warning: The safety and effectiveness of this device, when used in conjunction with other therapies, has not been established. (See Sections 4 & 5)
- Warning: The use of the Prosorba® column in patients receiving concomitant anticoagulation has not been studied.
- Warning: The safety and effectiveness of retreatment with the Prosorba® column has not been established.

Adverse Effects:

The most frequent adverse reactions reported in association with the use of the Prosorba® column include: joint pain, joint swelling, fatigue, paresthesias, headache, hypotension, anemia, nausea, sore throat, edema, abdominal pain, hypertension, rash, dizziness, diarrhea, hematoma, flushing, chills, respiratory difficulties, chest pain, and fever. Sepsis has also been reported. (See Section 6 and 7)

Other potential adverse reactions include those associated with any procedure involving extracorporeal blood circulation. These include blood loss from equipment or tubing leaks or as a result of improper use of anticoagulants, damage to blood cells or fluid balance mismanagement leading to hypertension or hypotension or arrhythmia. (See Section 6)

Maintaining Device Effectiveness: Use aseptic technique. Store in the range of 2-8°C. Do not reuse. Discard if packaging is damaged. (See Section 12.1)

Use in Specific Populations: Use of the Prosorba® column in children under the age of 18 or in pregnant women has not been studied. (See Section 8.1)

Patient Counseling Information: The patient should be advised of the possible adverse reactions known to be associated with the device. It is not unusual for the patient to feel tired after this type of therapy. RA patients should expect it will take a full treatment course before a therapeutic effect is noticed. RA patients may notice peri-treatment worsening of joint symptoms for several treatments, characterized by transient joint pain, fatigue and joint swelling (See Section 9 and refer to patient brochure).

How Supplied: The Prosorba® column is supplied, sterile, in case quantities of 6.

Distributed Exclusively by:
Fresenius Hemotechnology, Inc. 110 Mason Circle Suite A Concord, CA 94520-1238 800:909-3872

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INFORMATION FOR PRESCRIBERS

Caution: Federal Law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

1. BRIEF DEVICE DESCRIPTION

The Prosorba® column employs approximately 200 mg of protein A covalently bound to an inert silica matrix that is contained within a 300 ml polycarbonate housing. Each column contains 123 ± 2 grams of this matrix. Protein A is a component of certain strains of the *Staphylococcus* bacterium and it has propensity to bind immunoglobulin G (IgG) and IgG bound to an antigen, i.e., circulating immune complex.

2. INTENDED USE/INDICATIONS

- The Prosorba® column is indicated for use in the therapeutic removal of immunoglobulin G (IgG) and IgG-containing circulating immune complexes from plasma in patients with idiopathic thrombocytopenic purpura (ITP) having platelet counts less than 100,000mm^3.
- The Prosorba® column is indicated for use in the therapeutic reduction of the signs and symptoms of moderate to severe rheumatoid arthritis in adult patients with long-standing disease who have failed or are intolerant to disease-modifying anti-rheumatic drugs (DMARDs).

Contraindication: The use of this device is contraindicated in patients currently receiving angiotensin converting enzyme (ACE) inhibitor medications due to the incompatibility of these products with many procedures involving apheresis. A minimum 72-hour withdrawal period is recommended prior to administration of the Prosorba® column treatment. See the CONTRAINDICATIONS section for more information.

Warning: The use of central venous catheters in RA patients was associated with a > 40% rate of infection and/or local clotting. They should only be used with great caution. See WARNINGS below and Section 7 for more information.

3. CONTRAINDICATIONS

The use of this device is contraindicated in patients who:

- Are currently receiving angiotensin converting enzyme (ACE) inhibitor medications. ACE-inhibitors represent a potentially life-threatening risk to patients receiving treatments requiring extracorporeal blood procedures.
- Cannot tolerate therapeutic apheresis procedures and have demonstrated a prior hypersensitivity associated with therapeutic apheresis.
- Exhibit evidence of, or have a history of, hypercoagulability.
- Have pre-existing abnormalities of the coagulation system in which activation of the coagulation system may precipitate a thrombotic event, or recent history of thromboembolic events.

NOTE: ANGIOTENSIN RECEPTOR ANTAGONISTS ARE A DIFFERENT CLASS OF ANTIHYPERTENSIVES, AND TO OUR KNOWLEDGE DO NOT REQUIRE A WITHDRAWAL PERIOD.

4. WARNINGS

Warning: The Prosorba® column should be used with caution in patients:

- with inadequate peripheral venous access who require placement of a central venous catheter (see Section 7);
- where acute fluid shifts may precipitate congestive heart failure;
- with impaired renal function where expansion or reduction of plasma volume could be harmful;
- with clinically significant hypotension or borderline hypotension where a further fall in blood pressure could be harmful;
- with significant vascular disease where a fall in blood pressure could lead to significant post-obstructive physiologic abnormalities;

- with established or suspected intracranial disease where minor fluid shifts or pressure changes could exacerbate the underlying central nervous system problem;
- with severe anemia, i.e., Hct < 27, Hgb < 9;
- with systemic infection.

Warning: Should an adverse reaction occur requiring treatment termination and medical intervention, Prosorba® column therapy should not resume until the adverse reaction has dissipated and the patient has stabilized.

Warning: (FOR RA PATIENTS) Treatment with this device was associated with a drop in hemoglobin, hematocrit and MCV. Patients should be closely monitored for anemia during treatment and follow-up.

Warning: The safety and effectiveness of this device, when used in conjunction with other therapies, has not been established.

Warning: The safety and effectiveness of retreatment with the Prosorba® column has not been fully established.

Warning: The use of the Prosorba® column in patients receiving concomitant anticoagulation has not been studied.

Warning: The Prosorba® column is intended for single use only. Do not resterilize or reuse.

Warning: The safety and effectiveness of this device for pregnant women or patients under the age of 18 has not been established.

5. PRECAUTIONS

Caution: The safe and effective use of the Prosorba® column requires careful following of manufacturer's instructions and reference to the Section on "Individualization of Treatment" below.

Caution: Aseptic technique must be followed at all times.

Caution: If the package containing the column is damaged or the seal is broken, the column and its associated parts should not be used.

6. ADVERSE EVENTS

The most common adverse events observed with the use of the Prosorba® column in RA patients (i.e., those observed in more than 10% of the patients) are given in Table 1 below. These adverse events were observed in a study of 109 patients with RA. (See Section 7 for additional information).

Table 1- Most Common Adverse Events by Treatment Arm during RA Pivotal Study (N=109)

	Number/Percent of Patients w/ AE[1]		Number/Percent of Treatments w/ AE[2]	
Adverse Event (AE)	Prosorba	Sham	Prosorba	Sham
Joint Pain	46 (82%)	37 (70%)	249 (44%)	217 (45%)
Fatigue	31 (55%)	23 (43%)	103 (18%)	132 (27%)
Joint Swelling	29 (52%)	24 (45%)	137 (24%)	150 (31%)
Hypotension	21 (38%)	15 (28%)	40 (7%)	27 (6%)
Nausea	20 (36%)	15 (28%)	30 (5%)	28 (6%)
Pain, Abdominal	17 (30%)	12 (23%)	18 (3%)	14 (3%)
Flushing	16 (29%)	8 (15%)	20 (4%)	10 (2%)
Paresthesia	14 (25%)	12 (23%)	47 (8%)	24 (5%)
Headache	14 (25%)	10(19%)	36 (6%)	26 (5%)
Hematoma	14 (25%)	10 (19%)	19 (3%)	15 (3%)
Dizziness	13 (23%)	18 (34%)	22 (4%)	35 (7%)
Sore Throat	12 (21%)	7 (13%)	23 (4%)	12 (2%)
Rash	12 (21%)	4 (8%)	23 (4%)	12 (2%)
Diarrhea	12 (21%)	8 (15%)	14 (2%)	26 (5%)
Edema	11 (20%)	13 (25%)	29 (5%)	24 (5%)
Hypertension	10 (18%)	6 (11%)	26 (5%)	4 (1%)
Pain, Generalized	10 (18%)	9 (17%)	15 (3%)	14 (3%)

	Number/Percent of Patients w/ AE[1]		Number/Percent of Treatments w/ AE[2]	
Adverse Event (AE)	Prosorba	Sham	Prosorba	Sham
Chills	10 (18%)	7 (13%)	16 (3%)	15 (3%)
Dry Mouth	10 (18%)	0 (0%)	6 (1%)	0 (0%)
Nervousness	9 (16%)	11 (21%)	16 (3%)	22 (5%)
Anemia	8 (14%)	8 (15%)	29 (5%)	18 (4%)
Pain, Chest	8 (14%)	2 (4%)	10 (2%)	4 (1%)
Respiratory Difficulties	7 (13%)	5 (9%)	8 (1%)	5 (1%)
Fever	7 (13%)	12 (23%)	4 (1%)	9 (2%)
Muscle Tightness	6 (11%)	6 (11%)	14 (2%)	16 (3%)
Itching/hives	6 (11%)	3 (6%)	6 (1%)	9 (2%)
Infection	6 (11%)	5 (9%)	4 (1%)	7 (1%)
Twitching	2 (4%)	6 (11%)	6 (1%)	10 (2%)
Number of AE/pt	27.4	26.1		
Number of AE/pt-treatment			2.8	2.8

[1]Number of AE's includes those observed during treatment and assessment/follow-up visits.
[2]Number of AE's includes only those observed during the 12 treatments.

There were a total of 2,920 adverse events in study; 1,561 occurred in the Prosorba® treated patients and 1,359 occurred in the sham treated patients. Of the total adverse events, there were 44 serious complications (21 in 12 Prosorba® treated patients and 23 in 8 sham- treated patients) and 17 adverse events leading to hospitalizations (11 in the Prosorba® and 6 in the sham patients). Two deaths were observed during the study, both in the sham group. One death occurred nine months after treatment as a probable result of sequelae stemming from a central catheter infection. The second patient died seven months after treatment due to complications following surgery for cholecystitis.

The most common adverse events reported for ITP patients treated with the Prosorba® column (based on post-marketing medical device reports) are listed in Table 2 below.

Table 2 - ITP Historical Complaint Data (1987-1998)

Adverse Event Complaint	*Number of AE Complaints*	*% of Total Complaint AE's*
Hypotension	84	16
Nausea and/or Vomiting	59	11
Chills and/or Fever	55	11
Rash	43	8
Arthralgia	41	8
Vasodilatation (flushing)	33	6
Diarrhea	23	4
Abdominal Pain	18	3
Dyspnea	13	3
Chest Pain	11	2
Edema	7	1
Syncope	7	1
Tachycardia	7	1

Less frequent adverse events (i.e., those observed less than six times) include: lymphadenopathy, thrombosis, coagulation time increased, myalgia, vasculitis, cerebrovascular accident, headache, kidney failure, pain, pulmonary

edema, vascular purpura, amblyopia, back pain, cardiac arrest, cough increased, leukocytosis, vision abnormality, apnea, asthma, bradycardia, flu syndrome, laryngismus, purpura, thrombocytopenia, thrombophlebitis, vascular disorder peripheral, abnormal blood smear, anaphylaxis, anemia, angina, aphasia, bleeding, bone pain, cellulitis, cerebral infarction, coagulation disorder, coagulation time decreased, cyanosis, dermatosis, disseminated intravascular coagulation, gastrointestinal bleeding, grand mal seizure, hematuria, herpes zoster, hypertension, intracranial hemorrhage, laryngeal edema, leukopenia, neuropathy, paresthesia, petechiae, pulmonary emboli, sepsis, sweating, thrombocythemia, and vasculitic rash

Other potential adverse reactions include those associated with any procedure involving extracorporeal blood circulation. These include blood loss from equipment or tubing leaks or as a result of improper use of anticoagulants, damage to blood cells or fluid balance mismanagement leading to hypertension, hypotension or arrhythmia.

7. CLINICAL STUDIES

Idiopathic Thrombocytopenic Purpura (ITP):

The Prosorba® column is approved for idiopathic thrombocytopenic purpura (ITP). Retrospective case analysis suggests an overall response rate of 46% and further suggests that of responders, 80% had a durable response of one year.[1]

Rheumatoid Arthritis (RA):

Objective: The objective of this study was to evaluate the safety and effectiveness of Prosorba® column therapy in the treatment of patients with rheumatoid arthritis.

Study Design: This Phase III pivotal clinical trial, was a prospective, multi-center, randomized, double-blinded, sham-controlled study of patients with severe and active rheumatoid arthritis, who had failed or were intolerant to methotrexate and/or multiple DMARDs, with at least 20 tender and 10 swollen joints. This study was conducted in 1996 - 1998.

The design required that all patients entering the trial discontinue DMARD therapy prior to enrollment; one month prior for methotrexate and three months prior for other DMARDs. This "washout" trial design permitted less bias in the analysis of the effectiveness of the Prosorba® column in patients with rheumatoid arthritis who failed DMARDs. Stable, low doses of prednisone (≤ 10 mg/day) and non-steroidal anti-inflammatory drugs were permitted throughout the trial; however, dose changes were not permitted.

Patients studied: The baseline characteristics of the patients studied are presented in Table 3 and Table 4.

Table 3. Demographic characteristics of patients studied in RA pivotal clinical trial.

Characteristic	Sham group	Prosorba group
Number of subjects	47	52
Age (years)	52.4 ± 10.8	53.0 ± 10.4
Gender (female %)	71.1	82.4
Positive RF (%)	94	90
Prior disease duration (years) (mean)	17.4 ± 10.3	14.6 ± 10.0
Prior disease duration (years) (min/max)	2.4 - 42.6	1.7 - 50.6
Class III stage (%)	48.9	38.5
Previous treatment with methotrexate(%)	87	87
Prior DMARD regimens failed	5.5 ± 3.7	5.3 ± 6.0

[1] Snyder, HW et. al., Experience With Protein A - Immunoadsorption in Treatment-Resistant Adult Immune Thrombocytopenic Purpura, BLOOD, Vol. 79, No 9 (May 1), 1992:2237-2245.

Table 4 - Baseline ACR Criteria for patients enrolled in RA pivotal clinical trial.

Characteristic	Sham group	Prosorba group
Tender joint count (of 68)	36.2 ± 9.9	36.7 ± 9.2
Swollen joint count (of 66)	23.8 ± 9.6	23.9 ± 8.9
Physician assessment of disease activity (0-10)	7.6 ± 1.0	7.2 ± 1.3
Patient assessment of disease activity (0-10)	7.7 ± 1.1	7.5 ± 1.4
Patient assessment of pain (0-10)	7.6 ± 1.2	7.4 ± 1.5
Health assessment questionnaire (0-3)	1.9 ± 0.6	1.8 ± 0.5
C-reactive protein (mg/ dL)	4.0 ± 3.0	4.1 ± 4.0

Methods: Patients were randomized to receive a Prosorba® column treatment once a week for twelve weeks or a non-column (sham) apheresis procedure once a week for twelve weeks. A plasma volume of 1250 ± 250 mL was to be passed through the Prosorba® column for each session. Flow rates were 10 to 20 ml/min. The mean plasma volume treated for the Prosorba® column patients was 1239.8 ± 131.7 ml, while the mean plasma volume treated for the sham patients was 1233.1 ± 149.4 ml. At least 6 of the 12 treatments and all required follow-up visits had to be performed for patients to be included as completed in the analysis. Effectiveness determinations were based on intent to treat with the last observation carried forward.

Effectiveness determinations were made at trial weeks 5, 9, 13, 16, 19, 20 and 24 on all patients. If a patient was a non-responder at week 24, he or she was exited from the protocol. Information regarding adverse events was collected at weekly visits. Effectiveness was determined using the ACR Definition of improvement[2] at weeks 19/20.

The results are presented in Table 5. The ACR 20 response rate in patients treated with the Prosorba® column was 28.9% as compared to 10.6% for the sham group.

Table 5 - Primary Effectiveness Analysis

	Prosorba	Sham	Total
Patients enrolled	52	47	99
Withdrawn	16	15	31
Completed	36	32	68
# ACR responders	15	5	20
% ACR responders	28.9%	10.6%	20.2%
Triangular test adjusted p value	0.0309		
Unadjusted p-value**	0.031; 0.040		

** Chi square and Fisher's exact test

Of the 16 patients who withdrew in the Prosorba® column arm, 7 withdrew due to adverse events, 5 due to lack of effectiveness, 2 due to difficulties with blood access (involving central lines), 1 was discontinued due to protocol violations and 1 voluntarily withdrew. Of the 15 patients who withdrew in the sham arm, 5 discontinued due to adverse events, 4 for lack of effectiveness, 3 due to difficulties with blood access (central lines), 1 for protocol violations and 2 voluntarily discontinued.

[2] Felson DT et al. American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis. Arthritis Rheum 38:727, 1995.

Figure 1 (below) presents the number of responders in the Prosorba® column and sham groups over the course of the study.

Figure 1 - Percent of ACR 20 responders in Prosorba® column and sham arms over time.

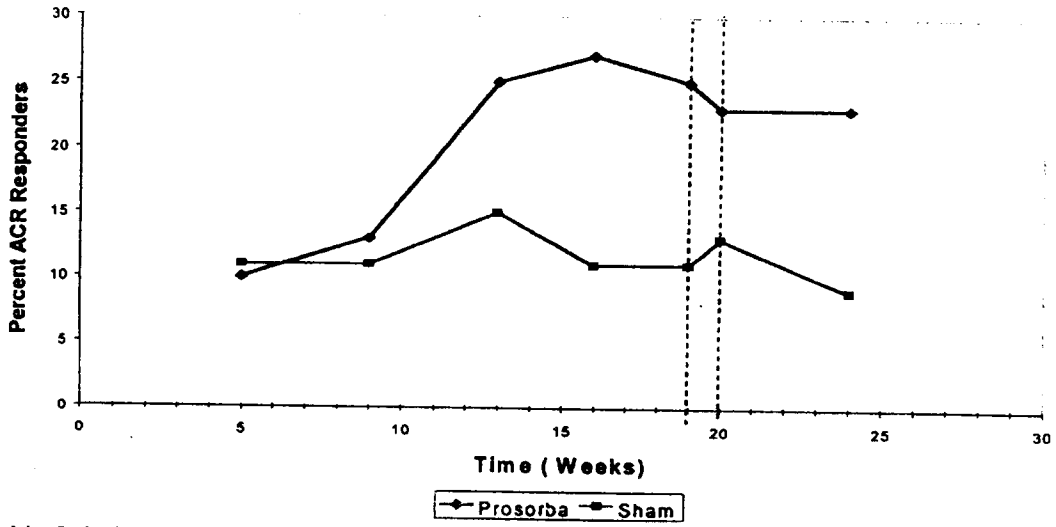


Table 6, below, shows the mean ACR component scores over time for both Prosorba® column and sham arms at weeks 19, 20 & 24.

Response duration of the Prosorba® column treated patients was calculated as a survival analysis, using the SAS LIFETEST procedure to determine mean and median survival (of response). The mean and median duration of improvement were 37.03 ± 5.3 weeks and 32 weeks, respectively.

Table 6 - Mean ACR Component Scores Over Time for Both Prosorba® column and Sham Arms at Weeks 19, 20 and 24 (n=99)

ALL PROSORBA PATIENTS (N=52)

	Baseline	*Week 19*		*Week 20*		*Week 24*	
Parameter	*Value*	*Average*	*Decrease*	*Average*	*Decrease*	*Average*	*Decrease*
Tender Joints	36.7	23.5	35.3%	23.3	36.8%	27.8	25.2%
Swollen Joints	23.9	18.3	24.9%	17.6	28.6%	20.1	15.4%
Patient Pain	7.4	5.4	24.4%	5.7	22.6%	6.5	11.1%
Patient Global	7.5	5.4	24.6%	5.5	23.4%	6	17.7%
MD Global	7.2	5.2	25.0%	5.9	16.5%	5.7	19.7%
HAQ	1.8	1.6	1.6%	1.6	3.5%	1.7	-0.6%
CRP	4.0	3.7	16.2%	3.6	18.9%	4	6.4%

ALL SHAM PATIENTS (N=47)

	Baseline	*Week 19*		*Week 20*		*Week 24*	
Parameter	*Value*	*Average*	*Decrease*	*Average*	*Decrease*	*Average*	*Decrease*
Tender Joints	36.2	34	10.3%	30.8	17.7%	31.6	15.3%
Swollen Joints	23.8	21.5	10.3%	19.6	18.9%	19.6	20.3%
Patient Pain	7.6	6.7	7.0%	6.7	7.5%	6.3	11.7%
Patient Global	7.7	6.8	7.5%	6.7	10.5%	6.3	13.3%
MD Global	7.6	6.3	15.7%	6.4	13.2%	6.4	13.2%
HAQ	1.9	1.8	4.4%	1.7	4.2%	1.7	7.3%
CRP	4.0	4.1	-9.8%	3.6	0.1%	3.5	2.1%

PROSORBA RESPONDERS (N=15)

	Baseline	*Week 19*		*Week 20*		*Week 24*	
Parameter	*Value*	*Average*	*Decrease*	*Average*	*Decrease*	*Average*	*Decrease*
Tender Joints	35.9	11.8	67.4%	12.1	65.5%	14.3	60.5%
Swollen Joints	24.0	12.2	53.1%	10.5	60.7%	13.9	42.9%
Patient Pain	7.7	3	60.3%	3.6	51.8%	4.8	37.5%
Patient Global	7.7	3.1	58.4%	3.4	52.4%	3.8	49.3%
MD Global	7.0	3.1	54.8%	4.2	38.7%	3.5	50.6%
HAQ	1.8	1.3	27.6%	1.3	27.4%	1.4	21.8%
CRP	3.5	2.6	19.8%	2.4	22.6%	2.8	0.1%

Safety

The most frequent adverse events are provided in Table 1 in Section 6 above. Adverse events that were observed in less than 10% of the patients included: tinnitus, insomnia, spasm, hypovolemia, bronchitis, sinusitis, vasovagal reactions/syncope, tachycardia, coagulation abnormalities/thrombosis, constipation, tremors, vomiting, gastritis, flu-like symptoms, cough, sepsis, injection site reaction, weight loss, muscle aches, palpitations, hair loss, joint stiffness, dental diseases, vasoconstriction, flatulence, arrhythmia, ear pain, neck pain, urticaria, bone pain, petechiae, red cell split, hemolysis, allergic reaction, photophobia, ACDA reaction, Baker's cyst, depression, dyspepsia, hyperthyroidism/elevated T4, hematuria, osteopenia, thrush, myasthenia, bloody nose, bradycardia, vitreous disease, hyperglycemia, hypokalemia, laryngitis, lymphadenopathy, pericarditis, rhinitis, glossitis, sweating, enlarged abdomen, back pain, ileitis, dysphagia, taste perversion, hair breakage, injection site pain, injection site hemorrhage, urinary tract infection, gastroenteritis, throat tightness, blurred vision, vasculitis, impaired concentration, agitation, amnesia, decreased renal function, dry eyes, incontinent bladder/bowel, labyrinthitis, malaise, mouth sores, polyuria, skin ulcer, amenorrhea, anorexia, melena, somnolence, skin discoloration, conjuctivitis, hyperkinesia, scleritis, thrombocytopenia, and bursitis.

A significant change over time was observed in hemoglobin, hematocrit and MCV. The trend was apparent in both the treatment and the control groups. The hematocrit fell from approximately 43 at baseline to 37 at week 24 and the average decrease in hemoglobin was 11.5% for the Prosorba® column group and 12.7% for the sham group. These changes are attributed to the apheresis procedure, the effects of blood drawing and to the anemia of chronic illness that is apparent for most RA patients. The changes over time for hemaglobin, hematocrit, MCV and RBC were not significantly different based on treatment group. One patient in the study (Prosorba® group) received a transfusion due to anemia related to the treatment.

Five of the nine patients who received central venous access lines experienced complications related to their use. Among these five patients were three sham-treated patients who developed infections: (1) one sham patient developed a localized catheter infection and thrombosis; (2) the second sham patient experienced infection and thrombosis at the catheter site with subsequent *Staphylococcal* sepsis; (3) the third sham patient developed secondary septic pulmonary emboli due to a central line infection. In addition, two Prosorba-treated patients experienced complications secondary to central lines: (1) one patient developed an irreversible thrombosis; (2) the second patient experienced an episode of catheter site hemorrhage, followed by irreversible thrombosis at a later treatment.

Two of the most commonly reported adverse events during the pivotal trial were joint pain and joint swelling. A post-treatment "flare" was characterized as an acute exacerbation of joint pain and swelling, with onset typically between 2 and 24 hours after treatment, usually lasting from 12 to 72 hours. It was determined that 19/52 (37%) of Prosorba treated patients and 13/47 (28%) of sham-treated patients reported at least one episode of a post-treatment flare.

A statistically significant change in platelet count over time was observed. This change (an apparent 8% increase) was the same in both treatment groups. A minimal baseline neutrophilia was also observed, similar in both treatment arms, thought to be secondary to underlying disease and steroid usage. This neutrophilia was stable and without change during the course of the trial. There were no changes in lymphocytes or bands during the course of the trial.

There were no significant changes over time in mean or median values of any of the tests used to assess hepatic or renal function. Serum electrolytes were all within normal limits, with no changes over time nor differences between treatment groups. INR and PTT mean and median values remained normal throughout the trial. The mean levels of fibrinogen were uniformly elevated but this was attributed to the patients' underlying disease. There was no significant change over time in fibrinogen levels and no differences were observed between the two groups.

8. INDIVIDUALIZATION OF TREATMENT

(FOR RA PATIENTS) In clinical studies, the Prosorba® column treatment was administered once a week for 12 weeks. Plasma volumes of 1250 ml ± 250 ml were processed during each treatment.

8.1 Use in Specific Populations

Use of the Prosorba® column in children under the age of 18 or in pregnant women has not been studied.

9. PATIENT COUNSELING INFORMATION

The patient should be advised of the possible adverse reactions known to be associated with the device. It is not unusual for the patient to feel tired after this type of therapy. RA patients should expect it will take a full treatment course before a therapeutic effect is noticed. As an aid in providing information to the physician to counsel patients, the expected results assuming completion of the prescribed treatment course was evaluated. In this analysis, 41.7% (15/36) Prosorba® column treated patients and 15.6% (5/32) sham treated patients responded. RA patients may notice peri-treatment worsening of joint symptoms for several treatments. All patients should be given a copy of the patient brochure.

10. CONFORMANCE TO STANDARDS

The Prosorba® column is manufactured according to current FDA Good Manufacturing Practices regulations.

11. HOW SUPPLIED The Prosorba® column is supplied, sterile, in case quantities of 6.

12. OPERATOR'S MANUAL

12.1 Maintaining Device Effectiveness

Use aseptic technique. Store in the range of 2-8°C. Do not reuse. Discard if packaging is damaged.

12.2 Complete Device Description

The Prosorba® column employs approximately 200 mg of protein A covalently bound to an inert silica matrix that is contained within a 300 ml polycarbonate housing. Each column contains 123 ± 2 grams of this matrix. Protein A is a component of certain strains of the *Staphylococcus* bacterium and it has the propensity to bind immunoglobulin G (IgG) and IgG bound to an antigen, i.e., circulating immune complex. Treated plasma that has been passed through the device can then be returned to the patient.

The Functional Components:

Protein A is a cell surface molecule discovered in staphylococcal bacteria that has specific binding affinity for the F_c region of immunoglobulin proteins. This multi-domained protein can bind several immunoglobulins simultaneously or several sites on a given immunoglobulin simultaneously, and is believed to be an important part of the bacteria's immune escape repertoire.

The Properties:

The implementation requires the use of a plasmapheresis device. The Prosorba® column is intended to present a covalently immobilized protein A matrix to the patient plasma, after which the plasma and cellular components are reinfused to the patient.

The Principles of Operation:

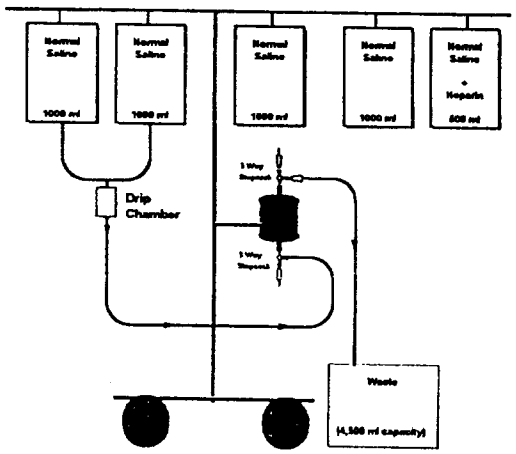
The principles of operation of the Prosorba® column are represented by the following four main steps in the use of the device: a) priming the Prosorba® column b) separating the plasma c) passing the plasma through the Prosorba® column, and d) reinfusing the treated plasma back into the patient.

12.3 Directions for Use

COLUMN PREPARATION (SALINE WASH AND ANTICOAGULATION):

Supplies

1. 4 liters of IV quality normal saline (NS)
2. 500 mL of IV quality normal saline with 5,000 units heparin
3. 3-Way luer lock stopcocks (2 each)
4. Y-type fluid administration set with drip chamber (1 each)
5. Non-vented secondary IV tubing with spike and needle adapter (1 each)
6. Waste bags capable of holding at least 4.5 liters of fluid in total
7. Prosorba® column holder (1 each)
8. Freestanding IV pole, i.e., not attached to apheresis device



Notes

1. Ensure that functional venous access to the patient is established before priming the Prosorba® column.
2. Use standard aseptic technique for all Prosorba® column tubing connections.
3. Maintain the Prosorba® column in a stable, upright position during preparation and treatment (except during agitation phase of priming).
4. Fluid flowing through the Prosorba® column must always be directed upward, i.e., fluid must enter the Prosorba® column at the base inlet and leave at the top inlet.
5. Ensure that the package containing the Prosorba® column is not damaged and the seal is intact.
6. If possible, the column should be primed at bedside and used without transportation. If a primed column must be transported, it is necessary to prevent agitation.

Saline Prime Procedure

1. Attach a Prosorba® column holder to a freestanding IV pole.
2. Remove the Prosorba® column from the package and set the column in the column holder.
3. Remove the end caps and attach a 3-way stopcock to each of the top and base inlets of the column.
4. Hang two bags of NS. Spike each bag with one line of the Y-type tubing set. Prime the Y-type tubing set with NS. Leave one line open and the other closed. Ensure that the clamp below the drip chamber is closed.
5. Attach the needle adapter end of the Y-type tubing set to the side port of the bottom stopcock. Position the lever on the bottom stopcock to permit fluid to flow from the tubing set into the column.
6. Attach the needle adapter end of the non-vented secondary IV tubing to the side port of the top stopcock. Position the lever on the top stopcock to permit fluid to flow from the column through the secondary IV tubing. Insert the spike end of the secondary IV tubing into a waste bag. Spike the first waste bag into a second waste bag and so on until the waste bags have a combined capacity that can hold at least 4.5 liters of fluid.
7. Begin priming the Prosorba® column with NS at approximately 20 mL/min. (discernible drips) by opening the clamp below the drip chamber.
8. When the NS has completely filled the column, pick up the column and roll it between the hands to ensure complete hydration of the matrix. Do not turn the column upside down. Do not tap the column. Be careful not to kink or disconnect any lines. Continue to roll the column until a total of 500 mL of NS has passed through it.
9. Place the column back in the column holder and do not disturb or move it again.
10. Fully open the clamps to both bags of NS to allow NS to flow to the column.
11. Replace the saline bags before they are completely empty. Do not let the IV lines run dry.

Anticoagulation Procedure

1. Once the 4 liters of NS have been perfused through the column, perfuse the 500 mL of NS with 5,000 units of heparin through the column at approximately 20 mL/min. (discernible drips). Do not move the column during this anticoagulation procedure.
2. Continue with the steps described in the Procedure Section below. If transport of the Prosorba® column to the treatment location is necessary, close the top and bottom stopcocks so they are off to the column.

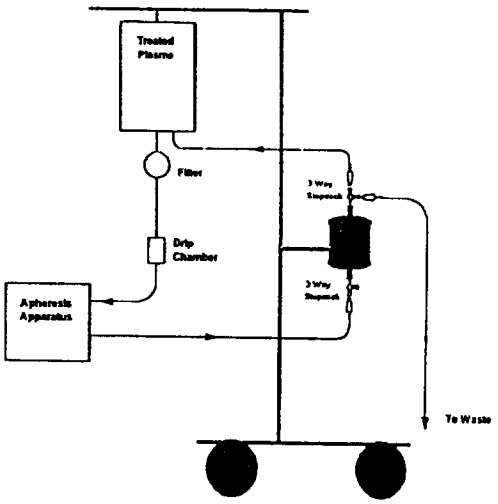
THE PROCEDURE:

Supplies

1. Apheresis machine, associated tubing, and appropriate connectors
2. 600 mL transfer pack with needle adapter (1 each)
3. Leukocyte removal filter which removes microaggregates, e.g., PALL PXL-8 (1 each)
4. Prosorba® column prepared per Column Preparation procedure

Perfusion Preparation

1. Set the prepared Prosorba® column (see Column Preparation) on a column holder attached to an IV pole.
2. Prepare the apheresis apparatus as indicated in the apparatus manufacturer's instructions, including establishment of patient blood access and anticoagulation.
3. Attach the leukocyte filter to the apheresis machine using the appropriate line. Prime this line and the filter with normal saline and spike the filter into the 600 ml transfer pack. Do not back prime the filter.
4. Attach the needle adapter from the transfer pack to the top port of the top stopcock on the Prosorba® column.
5. Connect the bottom stopcock of the Prosorba® column to the plasma collect line of the apheresis apparatus, using an appropriate non-vented line.



Perfusion Procedure

1. Initiate apheresis apparatus operation discarding the first 300 mL of fluid (NS + 5000 units of heparin) from the column to a waste container.
2. Re-establish plasma flow back into the patient by turning the lever on the top stopcock to direct plasma from the Prosorba® column to the transfer pack and through the filter.
3. Begin returning treated plasma to the patient at 10 mL/min. Monitor the patient's vital signs for 15 minutes. If the vital signs have remained stable, the plasma return flow rate can be increased to 15 mL/min. for 15 min. then to a maximum of 20 mL/min. Continue monitoring vital signs every 15 minutes. No more than 2000 mL of plasma should be treated per day per patient.
4. Terminate the on-line procedure with the following steps:
   a. displace the plasma remaining in the Prosorba® column with 250 to 300 mL of IV quality NS;
   b. infuse the displaced plasma into the patient at 10 to 20 mL/min.; and
   c. disconnect the patient from the apheresis apparatus as indicated in the apparatus manufacturer's instructions.

Patient Monitoring

1. Vital signs should be monitored prior to the procedure, during the procedure, after the procedure and for approximately 30-60 minutes thereafter. The patient should also be monitored throughout the process for adverse reactions.

How Supplied:

The Prosorba® column is supplied, sterile, in case quantities of 6.

Patient Labeling

What is the Prosorba® column ?

The Prosorba® column is a plastic cylinder about the size of a coffee mug that contains a sand-like substance coated with a special material called Protein A. Protein A is unique in that it binds certain elements from your blood called antibodies. Normally, antibodies protect you from disease. However, sometimes your body produces unwanted antibodies that attack your own body tissues. These unwanted antibodies can result in disease. The Prosorba® column works to counter the effect of these harmful antibodies.

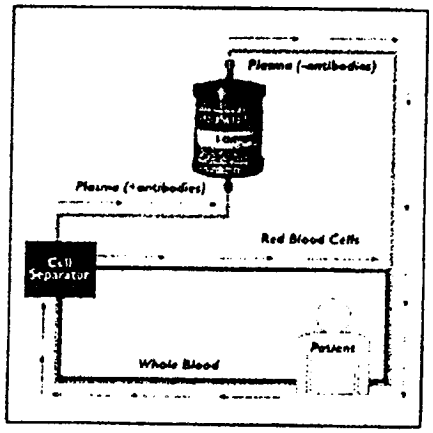
What is involved in the Prosorba® column treatment?

Normally, during therapy, blood is drawn from a vein in your arm and is then pumped into an apheresis machine, or cell separator. This machine separates the liquid part of your blood (the plasma) from the blood cells. Your plasma passes through the Prosorba® column, out through another tube and, after being reunited with your blood cells, is returned to your body through a vein in your other arm (see the diagram). The entire procedure treats 4-8 cups of plasma and takes approximately 2 hours.

How often is the procedure performed?

How often you receive these treatments is based upon your condition. Twelve treatments, once per week for 12 weeks are recommended for patients with rheumatoid arthritis (RA). The recommended treatment for patients with idiopathic thrombocytopenic purpura (ITP) is more variable and may range from daily to weekly treatments. Your physician will advise you of the best method of treating your disease.

How will I know if the procedure is working?



Like other therapies, the response to treatment will vary from person to person and your doctor will closely monitor your progress. Not all patients respond to Prosorba® column treatments. Patients with RA should not expect any evidence of improvement until a full course of treatments have been received. This delayed reaction is normal and you should not be concerned that the treatment isn't working. It may take this long for your body to respond. Our clinical study has demonstrated that those patients who do notice improvement may continue to experience reduced symptoms for some months after completion of the treatments. Patients with ITP may show improvement after only a few treatments, but commonly require 6 treatments to obtain the best results.

What about the side effects?

When they occur, the side effects of the Prosorba® column are usually temporary and manageable. The most common side effect is a "flu-like" condition with chills, mild fever, nausea and joint/muscle pain. Your physician may prescribe medications to make you more comfortable. In our clinical study, patients with rheumatoid arthritis often experienced some fatigue and a temporary increase in joint pain and swelling for a day or two after treatment. The process of removing your blood for treatment may cause a temporary drop in your blood pressure. In such cases, the doctor administering the apheresis treatment may decide to slow down the blood flow or give you additional fluids by vein.

As with any medical therapy, you should always report any rash or other unusual symptoms to your doctor as soon as possible. Please read the IMPORTANT PATIENT INFORMATION on the back panel of this pamphlet.

If I am treated as an outpatient, will I be able to return home after each treatment?

Yes, if you are not already staying overnight in the hospital because of your underlying condition, you will normally return home after each treatment.

How shall I care for myself after the treatment?

It is not unusual to feel tired after this type of treatment. Your physician may recommend rest for some time after the treatment.

Additional Patient Information About the Prosorba® column

IMPORTANT PATIENT INFORMATION

Your physician has been supplied with full and complete prescribing information advising him/her of the best way to use the Prosorba® column. The summary below includes an abbreviated version of this information for your review.

For what conditions is the Prosorba® column used?

The Prosorba® column is approved for use in the treatment of some patients with idiopathic thrombocytopenic purpura (ITP) and for some patients with rheumatoid arthritis (RA) who are not responsive or are intolerant of DMARD therapy. Both diseases are conditions brought about by an abnormal situation in the body's antibody system. Your doctor has made a determination that you may benefit from a course of Prosorba® column treatments.

For what conditions should the Prosorba® column not be used?

Heart conditions or high blood pressure: You should *never* participate in a Prosorba® column treatment program if you are currently taking or have recently (within a week or so) taken angiotensin-converting-enzyme medications. These medications are often referred to as "ACE inhibitors" and would normally be prescribed to you if you have been experiencing heart problems or high blood pressure. If you have either of these conditions or related conditions, talk to your doctor before starting the Prosorba® column treatments.

Blood Clotting Problems: Tell your physician if you have experienced strokes or blood clotting.

Pregnancy: The use of the Prosorba® column has not been studied in pregnant women.

What if I have problems after my treatment when I have returned home?

Although rare, unusual reactions to the Prosorba® column do occur. You should always report unusual symptoms to your doctor. Any rash should be reported since it may (rarely) signal a reaction called *vasculitis* which requires discontinuation of the Prosorba® column treatments.

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