# LIPOSORBER® LA-15

# LDL ADSORPTION COLUMNS

Instructions for use in adult and pediatric Focal Segmental Glomerulosclerosis (FSGS)

# FSGS

# **Humanitarian Use Device**

Authorized by Federal (USA) law for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

**Caution:** Federal law restricts this device to sale by or on the order of a physician.

Carefully review the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" and use only under the direction of a licensed physician with appropriate training.

# Kaneka

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# I. Introduction

The LIPOSORBER® LA-15 LDL Adsorption Column set is one of three disposable device components of the LIPOSORBER® LA-15 System. It is comprised of two LIPOSORBER® LA-15 LDL Adsorption Columns, each containing 150 ml of dextran sulfate cellulose adsorbent.

The technical characteristics of the LIPOSORBER® LA-15 LDL Adsorption Columns are explained in Section III of this instructions for use.

Before using the LIPOSORBER® LA-15 LDL Adsorption Column, carefully review this instructions for use and the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" (hereinafter referred to as "Operator's Manual for FSGS").

# II. Indication

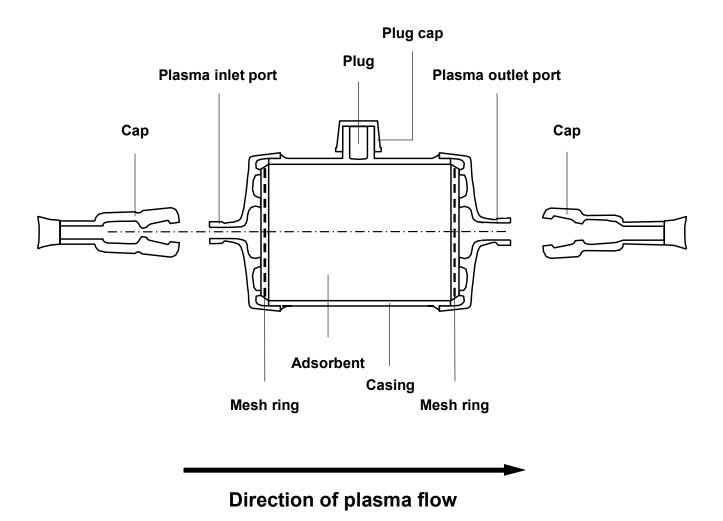
The LIPOSORBER® LA-15 System is indicated for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- standard treatment options, including corticosteroids and/or calcineurin inhibitor, treatments are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.



# **III. Technical Characteristics**

# LIPOSORBER® LA-15 LDL Adsorption Column



	LIPOSORBER® LA-15 LDL Adsorption Column (2 pieces)
Material	Adsorbent: Dextran sulfate cellulose gel (150 mL each) Casing: Polycarbonate
Filling Liquid	Sodium citrate/citric acid solution
Sterilization Method	Steam autoclave at 121°C for 20 minutes

**FSGS** 

# IV. Operations

Carefully review the "Operator's Manual for FSGS" and use only under a physician's direction. **Do not reuse.** 

Use of the LIPOSORBER® LA-15 System in adult and pediatric patients with FSGS is recommended to occur twice weekly for 3 weeks followed by once per week for six weeks.

# V. Contraindications

The LIPOSORBER® LA-15 System must not be used in:

1. patients who have been treated with angiotensin-converting enzyme (ACE) inhibitors within the past 24 hours;

Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER® LA-15 LDL Adsorption Column under concomitant ACE inhibitor medication. The risk of an anaphylactoid reaction may be minimized by withholding the administration of ACE inhibitors for approximately 24 hours before each LDL-apheresis procedure. The time period to withhold ACE inhibitors should be prolonged, if determined by the treating physician, considering each individual's renal function and the biological half-life of the ACE inhibitor currently in use. If required, ACE inhibitor administration may be resumed on the day of the apheresis treatment but only after the apheresis treatment is complete.

- 2. patients for whom adequate anticoagulation cannot be achieved, such as those with severe hemophilia, severe hemorrhage diathesis, severe gastrointestinal ulcers, or who are receiving vitamin K antagonist medications after surgery;
- 3. patients for whom extracorporeal circulation therapy with the LIPOSORBER® LA-15 System cannot be tolerated such as those with severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, acute apoplexy, or severe uncontrollable hypertension or hypotension; and
- 4. patients with hypersensitivity to dextran sulfate cellulose, heparin or ethylene oxide.

# VI. Patient Selection

The following patients may benefit from the LIPOSORBER® LA-15 System. The following are intended only as guidelines for appropriate patient selection:

- Adult and pediatric patients with GFR ≥ 60 ml/min/1.73 m² and a history of primary FSGS accompanied by refractory or recurrent nephrotic syndrome defined as:
  - Patients unresponsive to standard corticosteroid and/or calcineurin inhibitor therapy for at least 8 weeks resulting in failure to achieve complete or partial remission.

or

 Patients intolerant to standard therapies due to severe side effects which negatively affect quality of life without providing an acceptable level of clinical benefit.

or

Patients in whom standard therapies are contraindicated.

OR

 Adult and pediatric post renal transplantation patients with nephrotic syndrome associated with primary FSGS.

# VII. Warnings

- 1. Before using the LIPOSORBER® LA-15 System, including the LIPOSORBER® LA-15 LDL Adsorption Column, carefully review the instructions for use provided for each of the disposables and the "Operator's Manual for FSGS". Persons performing the procedures must be qualified to perform extracorporeal procedures, and have completed the required training program. Users should follow all operating or maintenance procedures published by Kaneka Pharma America LLC and use only the disposable device components recommended by Kaneka Pharma America LLC. Failure to do so may result in injury or loss of life.
- 2. LDL-apheresis treatment of patients who have taken any antihypertensive drugs within 24 hours of treatment may cause hypotension in such patients. When clinically feasible, patients should not receive antihypertensive drugs during the 24-hour period prior to undergoing the LDL-apheresis procedure. Before each treatment, physicians should determine when patients took their last dose of such medication.
- 3. The storage and use of this disposable device other than in accordance with the instructions published by Kaneka Pharma America LLC or the use of disposable device components not recommended by Kaneka Pharma America LLC may result in serious patient injury or loss of life. The manufacturer and distributor(s) of this device will not be responsible for patient safety if the procedures to operate and maintain the LIPOSORBER® LA-15 System are other than those specified in this instructions for use and the Operator's Manual for FSGS.

FSGS

- 4. During an LDL-apheresis procedure, 0.9% Sodium Chloride Injection, USP, 5% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP, and Heparin Sodium Chloride Injection, USP, are used. Carefully identify each solution and ensure that it is properly connected to the LIPOSORBER® LA-15 System. Using the incorrect solution may result in serious injury or possible death.
- 5. The LIPOSORBER® LA-15 LDL Adsorption Column is disposable and is **intended for use in a single use only**. **Never reuse**. Discard this disposable after each use.
- 6. The LIPOSORBER® LA-15 System may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended to at all times by a physician or qualified health-care professional adequately trained in all aspects of the procedure.
- 7. Rinsing and subsequent priming of the fluid pathway of the LIPOSORBER® LA-15 LDL Adsorption Columns with appropriate solutions are necessary before commencing the procedure. Because air bubbles in the LDL Adsorption Columns may lead to complications such as coagulation of plasma and impairment of performance, give full attention to measures that will prevent air bubble migration into the columns during rinsing and priming.
- 8. While operating, the differential pressure across the LIPOSORBER® LA-15 LDL Adsorption Column must be **under 100 mmHg**. If the differential pressure across the column rises extremely, the blood flow rate and/or plasma separation rate should be lowered appropriately or even stopped if necessary.
- 9. Citrate preparation (ACD) should never be used as an anticoagulant in the system. The LIPOSORBER® LA-15 System is designed solely for treatment using heparin as an anticoagulant. Anticoagulation is required to prevent thrombus formation from occurring within the extracorporeal circuit. Anticoagulation with too much heparin is associated with an increased risk of bleeding for the patient, especially after the procedure. In order to reduce the risk of bleeding, the puncture sites should be sufficiently compressed so that bleeding is stopped (See Operator's Manual for FSGS at Section 1.7 Adverse Events). In some patients the potential for development of a coagulopathy extending several days post-therapy may exist. In addition to adjusting heparin dosage based on clinical observation during and after the apheresis procedure, Activated Clotting Time and/or partial thromboplastin time (PTT) values may be used (See Operator's Manual for FSGS at Section 1.9.2 Instructions for Use regarding "Determining Heparin Dosage").
- 10. To minimize the risk of air embolism, the return tubing line must be connected to the air bubble detector.
- 11. No chemicals or solvents are to be used either inside or outside of this disposable device.
- 12. Due to the risk of reduction of blood pressure with the LIPOSORBER® LA-15 System, extra caution should be exercised in use of the system in patients with systolic and/or diastolic blood pressure  $\leq 5^{th}$  percentile for age, gender and height.
- 13. Use special caution in patients where the extracorporeal volume of approximately 400 ml potentially will exceed 10% of the patient's total blood volume. Such patients are at higher risk of experiencing hypovolemia, which is sometimes followed by hypotension.
- 14. In case of a power failure or system shutdown, terminate the procedure immediately according to the instructions provided in Section <u>7.6 Manual Blood Return</u> of the Operator's Manual for FSGS.



- 15. The safety of LDL-apheresis treatment with the LIPOSORBER® LA-15 System occurring more than twice a week or for treated volumes larger than 60mL/kg patient plasma volumes in FSGS has not been established.
- 16. Do not apply whole blood directly to the LIPOSORBER® LA-15 LDL Adsorption Column. This device is designed for perfusion of plasma only.
- 17. Make sure that the plasma flows in the direction of the arrow on the label of the LIPOSORBER® LA-15 LDL Adsorption Column.

# VIII. Precautions

- 1. The need for the administration of angiotensin receptor blockers (ARBs) prior to the treatment on the day of the apheresis treatment should be determined by the treating physician. If the treating physician determines that it is not necessary, the patient should not take ARBs on the day of the apheresis treatment until the apheresis treatment is completed in order to minimize the risk of a hypotensive reaction during the extracorporeal therapy.
- 2. Medical personnel should monitor the patient for adverse symptoms at all times during treatment and should be trained as to the protocol for responding with appropriate interventions (See Operator's Manual for FSGS at Section <u>1.7 Adverse Events</u>).
- 3. All connections of the extracorporeal circuit should be checked carefully prior to initiating and during the procedure. Avoid unnecessary kinking of the tubing lines and the patient's vascular access devices at all times.
- 4. The transducer protectors must be attached and locked to the machine and tubing lines. Strict aseptic technique should be used during this and all procedures. After the completion of the procedure, properly dispose of all used and unused transducer protectors. Do not reuse.
- 5. Each tubing line must be properly connected and cleared of air, prior to the start of Rinse. Do not allow air to be trapped in the set. Puncturing tubing lines may cause air embolism.
- 6. Drip chambers in the extracorporeal circuit should be kept at least  $\frac{2}{3}$  to  $\frac{3}{4}$  full and monitored at all times in order to decrease the risk of air embolism.
- 7. The fluid circuit of this system is intended to be sterile and nonpyrogenic. Aseptic handling techniques are necessary to maintain these conditions. Prior to use, carefully examine the packaging of the LIPOSORBER® LA-15 Column Set to ensure that it is intact and undamaged. Do not use the LIPOSORBER® LA-15 LDL Adsorption Column if the package, sterile bag, protective cap or the product itself is not intact or is damaged. Do not open the bags containing the LIPOSORBER® LA-15 LDL Adsorption Column until immediately prior to use.
- 8. The safety and probable benefit of LDL-apheresis using the LIPOSORBER® LA-15 System in FSGS have not been established for: (1) patients less than 21 kg in body weight; (2) patients less than 5 years of age; (3) patients with certain cardiac impairments such as uncontrolled arrhythmia, unstable angina, decompensated congestive heart failure or valvular disease; and (4) patients with thyroid disease or liver abnormalities.
- 9. The safety and probable benefit of LDL-apheresis using the LIPOSORBER® LA-15 System in FSGS has not been established for pregnant women or for women during the lactation period, e.g. the effect of treatments on folic acid levels has not been determined.



- 10. Closely monitor patient clotting time periodically during the procedure to ensure that an adequate level of anticoagulation is maintained.
- 11. Instructions for heparin administration should be followed as stated in the guidance provided by the manufacturer in the Operator's Manual for FSGS. The amounts of heparin outlined in the Operator's Manual for FSGS are intended as general suggestions. The exact amount, frequency and method of administration of heparin are the sole responsibility of the prescribing/attending physician and should be selected based on the individual patient's clinical condition.
- 12. Physicians and operators should follow the OSHA and the CDC/ACIP Adult Immunization Guidelines for Hemodialysis Patients. It is recommended that patients be screened for Hepatitis B and other infectious diseases; however, due to possible exposure to hepatitis virus, human immunodeficiency virus, and other infectious agents when handling extracorporeal blood circuits, blood or blood products, universal precautions should be taken at all times to prevent the exposure to and transmission of such agents.
- 13. When disposing of the disposable device components and wastes, comply with all local requirements and the policies of the facility regarding precautions for and prevention of infection and environmental pollution.
- 14. In transporting and storing the disposable, handle with care. Store the disposable in a clean and secure area at room temperature (5-30°C), avoiding exposure to direct sunlight, high humidity or excessive vibration. Handle the LIPOSORBER® LA-15 LDL Adsorption Column with care to avoid dropping or other sudden impacts and never allow it to freeze. Do not use an LDL Adsorption Column that may have been dropped, damaged or frozen.
- 15. The expiration date of the LIPOSORBER® LA-15 column is 4 years from the sterilization date. The LIPOSORBER® LA-15 column must never be used after the expiration date.
- 16. The LIPOSORBER® LA-15 System includes a blood warmer with a temperature setting range of 35-40 °C. It is recommended that the blood warmer be set at a temperature between 36-38 °C in order to avoid significant decreases in blood temperature during extracorporeal circulation.
- 17. Anemia may be minimized by the appropriate use of iron supplements.

# IX. Clinical Data

Clinical data to support the safety and probable benefit of LIPOSORBER® LA-15 System for FSGS can be divided to pre-transplant FSGS and post-transplant FSGS.

# 1. Adults

Published Clinical Studies of LIPOSORBER® LA-15 System Treatment for Patients with Nephrotic Syndrome (NS) and FSGS in adults are summarized in the table below.

Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre- transplant or Post- transplant
Muso 2015 [1] Muso 2015 [2]	44 (26 with FSGS)	Prospective Multicenter Single arm	Immediate to 2 years after treatment	Urinary Protein (UP) decreased from 6.28 ± 2.96 to 3.46 ± 3.34 g/day.  21/44 patients (48%) had a favorable 2-years outcome.	Pre- transplant
Muso 2001 [3] Muso 1999 [4]	17 (14 with FSGS)	Prospective Multicenter Controlled	Immediate to 2 years after treatment	UP decreased from 6.2 ± 3.3 to 2.7 ± 2.7 g/day.  The rate of achieving complete or incomplete remission was 71%.  As for the 2-years outcomes, 13/17 patients (76%) maintained UP <1.0 g/day.	Pre- transplant
Yokoyama 2002 [5]	6 (2 with FSGS; 1 treated with LIPOSO RBER®)	Prospective Single Center	Unknown	This was a prospective study of the effects of lymphocytapheresis in treating various forms of NS in 6 patients. One patient with FSGS failed to respond to one month of LIPOSORBER® treatment.	Pre- transplant
Nakamura 2006 [6]	8 FSGS	Prospective Single Center	2 weeks	UP decreased from 8.8 ± 4.2 g/day to 2.0 ± 1.2 g/day.	Pre- transplant
Muso 2007 [7]	41 FSGS	Retrospectiv e	5 years	At 1 month after LDL apheresis UP was significantly decreased.  Remission of nephrotic syndrome was observed in 18/29 patients (62%) followed at 2 years and 13/15 patients (86%) followed at 5 years.	Pre- transplant and Post- transplant



Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre- transplant or Post- transplant			
Case Studie	Case Studies							
Masutani 2005 [8]	1 FSGS	Case Report	1 year	LIPOSORBER® in conjunction with drug treatment resulted in reduction of UP from 6.8 g/day to 2.0 g/day.  Incomplete remission had been maintained for more than 1 year.	Post- transplant			
Miura 2009 [9]	1 FSGS	Case Report	40 days	Six cycles of hemodialysis were performed in conjunction with 4 cycles of LIPOSORBER® treatment. UP and serum creatinine levels recovered to normal values, and UP became undetectable by 40 days post-treatment.	Pre- transplant			
Miyazono 2008 [10]	1 FSGS	Case Report	Unknown	After 6 treatment sessions, the patient's UP decreased to non-nephrotic level. Furthermore, the patient's hypoproteinemia improved and renal function returned to normal. Although the patient experienced a relapse of nephrotic syndrome, 6 more sessions of LIPOSORBER® treatment brought the UP down to 0.8 g/day.	Pre- transplant			
Tsukada 2006 [11]	1 FSGS	Case Report	Unknown	The patient underwent 8 sessions of treatment using LIPOSORBER®, which resulted in the reduction of the UP level and improvement of renal functions.	Post- transplant			
Haikal 2016 [12]	1 FSGS	Case Report	5 months	Partial remission sustained 5 months post therapy	Pre- transplant			

- 1) Pre-transplant FSGS
- (i) Muso et al. (2001) [3]: This study describes the comparison of efficacy between the treatment with the LIPOSORBER® LA-15 System in combination with steroids (LDL-A group) and that with steroids only (steroid monotherapy (SM) group) for patients with nephrotic syndrome who did not respond to full-dose (prednisolone, daily 1 mg/kg b.w.) therapy of 1-month duration under the fixed treatment protocol. The LDL group consisted of 17 patients (FSGS: 14, minimal change nephrotic syndrome (MCNS): 3) who were treated with the LIPOSORBER® LA-15 System. Treatments were performed twice a week for 3 weeks followed by weekly treatment for 6 weeks. The SM group included 10 patients (FSGS: 9, MCNS: 1) who were treated only with continuous full-dose steroids.

## Results

## Effectiveness:

- Total cholesterol (TC) level in the LDL-A group was significantly decreased after the treatment (337±118 to 242±45.2 mg/dL, p=0.006), whereas decrease of TC level in the SM group was not significant (448±106 to 366±159 mg/dL, p=0.169).
- Hypoalbuminemia significantly improved in the LDL-A group (2.7±0.7 to 3.1±0.7 g/dL, p=0.014), while almost no change was noted in the SM group (2.8±0.4 to 2.9±0.7 g/dL, p=0.822).
- Proteinuria was significantly ameliorated in the LDL-A group (6.2±3.3 to 2.7±2.7 g/day, p=0.0008), while significant amelioration of proteinuria was not observed in the SM group (8.7±4.0 to 8.2±7.7 g/day, p=0.85).
- Average duration needed for a decrease of urinary protein to <3.5 g/day was significantly shorter in the LDL group than in the SM group (14.7±19.6 days vs 47.8±6.9 days, p=0.002).
- At the end of the treatment period, 9 patients (52%) in the LDL-A group achieved urinary protein level <1.0 g/day, whereas only 1 patient (10%) showed the same level in the SM group.
- As for the long-term outcomes (2 years after the end of the treatment period),
   13 out of 17 patients (76%) maintained urinary protein level <1.0 g/day in the LDL-A group, compared to only 2 in 9 patients (22%) in the SM group.</li>

## Safety:

The incidence of adverse events was not reported.

## Conclusion

Superiority of therapeutic efficacy of the treatment with the LIPOSORBER® LA-15 System in combination with steroids to that with steroids alone was demonstrated in controlled study.

This study was a follow-up of the multicenter study reported by Muso et al (Kidney Int) in 1999. In this study, the authors did not report any adverse events.

Summary: Among the 17 patients with FSGS, short-term and medium-term efficacy data were provided compared to controls. Adverse events were not mentioned in the report.



(ii) Nakamura et al. (2006) [6]: This study investigated the effect of LIPOSORBER® LA-15 System in treating FSGS as part of a larger study to determine whether the levels of urinary liver-type fatty acid-binding protein (L-FABP) are associated with the severity of nephrotic syndrome. At the beginning of the study, all FSGS patients received 60 mg/day prednisone for 6 months, followed by either cyclophosphamide or mizoribine for another 6 months. Treatment with LIPOSORBER® LA-15 System was performed in 8 patients with drug-resistant FSGS twice a week for 3 weeks, then once a week for 6 weeks. In each 3-hour treatment session, 3000-4000 mL of plasma were treated. Renal function in terms of daily urinary protein excretion and serum creatinine levels were measured before the start of treatment and 2 weeks after the final treatment session.

## Results

## Effectiveness:

- Comparing the clinical parameters before and after the treatment, urinary protein and serum creatinine decreased significantly from 8.8 ± 4.2 g/day to 2.0 ± 1.2 g/day (p < 0.01) and from 123.8 ± 26.5 µmol/L to 97.2 ± 17.7 µmol/L (p < 0.05), respectively, and total protein increased from 40 ± 8 g/L to 60 ± 9 g/L (p < 0.01).</li>
- In addition, serum level of L-FABP decreased from 122.6  $\pm$  78.4  $\mu$ g/gCr to 64.4  $\pm$  43.8  $\mu$ g/gCr (p < 0.05).

# Safety:

 The article did not report any adverse events associated with LIPOSORBER<sup>®</sup> LA-15 System.

## Conclusion

This study demonstrated that LDL apheresis therapy with LIPOSORBER® LA-15 System ameliorated proteinuria, hypoproteinemia, and renal function in drug-resistant FSGS.

This was a prospective study. Among the 8 patients with FSGS, encouraging short-term efficacy data were provided. A control arm was not included in this study. Adverse events were not mentioned in the report.

(iii) Muso et al. (2015) [1]: The investigators conducted a prospective, observational, multi-center cohort study (POLARIS study). In the POLARIS study, patients with nephrotic syndrome who did not respond to primary medication were registered before starting the treatment with LIPOSORBER® LA-15 System and clinical effectiveness and safety were examined. A total of 58 patients (who underwent 64 treatments) were registered in the study. Of the 64 treatment regimens, 17 were excluded for various reasons, leaving 47 treatment regimens for 44 patients available for analysis. As for FSGS, 23 patients were registered and underwent a total of 26 treatments. Clinical data were collected at baseline and after treatment with LDL-apheresis based on 24-hour urinalysis. Lipid profiles and clinical parameters were compared between before and after the treatment.

## Results

#### Effectiveness:

- TC and LDL cholesterol (LDL-C) levels were significantly decreased after the treatment (331.10 ± 113.25 to 210.38 ± 77.4 mg/dL; p<0.01, 205.86 ± 100.to 84 92.37 ± 56.64 mg/dL; p<0.01, respectively), whereas the changes of triglyceride (TG) and HDL-cholesterol (HDL-C) were not significant (262.74 ± 155.17 to 241.30 ± 182.14 mg/dL; n.s., 69.49 ± 22.58 to 73.64 ± 23.40 mg/dL; n.s.).</li>
- Hypoproteinemia (serum protein), hypoalbuminemia (serum albumin), and proteinuria (urinary protein) were significantly ameliorated immediately after treatment (4.42 ± 0.69 to 4.68 ± 0.81 g/dL; p<0.05, 2.15 ± 0.63 to 2.63 ± 0.79 g/dL; p<0.01, and 6.28 ± 2.96 to 3.46 ± 3.34 g/day; p<0.01, respectively). In addition, renal function (creatinine clearance) significantly improved immediately after treatment (58.59 ± 41.35 to 65.11 ± 41.39 mL/min; p<0.05).</li>
- Serum levels of fibrinogen and thrombin-antithrombin III complex (TAT) level were significantly reduced (374.46 ± 130.04 to 297.92 ± 108.87 mg/dL; p<0.01, 16.39 ± 33.60 to 12.21 ± 34.10 ng/mL; p<0.05, respectively) suggesting that treatment with LIPOSORBER® LA-15 System exerts anticoagulation activity.</li>

## Safety:

The incidence of adverse events was not reported.

## Conclusion

LDL apheresis therapy with LIPOSORBER® LA-15 System rapidly ameliorated symptoms of nephrotic syndrome i. e. proteinuria and hypoproteinemia in more than half of the patients who failed to respond to primary medication.

This was a short-term study.

The endpoints were:

- Complete remission: Urinary Protein (UP) = undetectable
- Incomplete Remission I: UP < 1.0g/day</li>
- Incomplete Remission II: 1.0 g ≤ UP < 3.5 g/day
- No effect: UP ≥ 3.5 g/day

In this study, complete or incomplete remission were considered favorable outcomes.

The average number of apheresis sessions was 9.6/patient. An average of 3.5 L of plasma was treated per session. Among the 44 patients, FSGS was the diagnosis in 23 (52.3%) of the patients.



(iv) Muso et al. (2015) [2]: The long-term (2 years) outcome of the POLARIS cohort was investigated for the 44 subjects. Of the 58 patients who were registered in the POLARIS study, 5 were excluded from the study because of protocol violation or inadequate data collection, 6 were lost to follow up, and 3 died during the follow-up period, thus leaving 44 subjects eligible for analysis at two years. As for primary diseases of the subjects, FSGS was found in the majority of cases, presenting in 28 subjects (63.6%).

## Results

## Effectiveness:

- Twenty-one (21) of the 44 subjects (47.7%) had a favorable outcome, with 11 subjects (25%) in complete remission (defined as urinary protein undetectable) and 10 subjects (22.7%) in incomplete remission I (defined as urinary protein level < 1.0 g/day). Twenty-three (23) subjects (52.3%) had an unfavorable result, with 11 (25%) in incomplete remission II (defined as 1.0 g/day ≤ urinary protein < 3.5 g/day) and 12 (27.3%) with no effect (defined as urinary protein level ≥ 3.5/day).</p>
- An analysis was performed of the factors affecting outcome. The authors found that the urinary protein level post-treatment was strongly associated with 2-year outcome (p < 0.001). For subjects with favorable outcomes, the urinary level after treatment was 1.68 ± 1.76 g/day compared to 6.18 ± 3.24 g/day for subjects with unfavorable outcomes.
- Improvement of parameters representing disease conditions of nephrotic syndrome, including serum albumin, eGFR, urinary protein and total and LDL cholesterol were all significantly associated with favorable outcome. This suggests that an early rapid alleviation of nephrotic syndrome by LDL-apheresis contributes to a favorable outcome.

## Safetv:

 No adverse event associated with LIPOSORBER® LA-15 System was reported in this report.

## Conclusion

The POLARIS study demonstrated that LDL apheresis therapy with LIPOSORBER® LA-15 System ameliorates nephrotic conditions and that the therapeutic efficacy of LDL apheresis was largely maintained for two years.

During the time from the short- to long-term POLARIS study, 3 subjects died of diseases unrelated to NS (cerebral infarction, lung cancer and pneumonia). Given the variety of histological diagnoses in the patients included in the study, it was challenging to ascertain the outcomes for patients with FSGS versus those with other diseases. That said, the study does report that urine protein levels decreased significantly and similarly for patients with/without FSGS and this study provides reasonable assurance of efficacy of the device in about 50% of patients with FSGS.

# 2) Post-transplant FSGS

<u>Muso et al. (2007) [7]:</u> This study describes 41 patients with refractory FSGS. The study population included a sub-set of 7 patients who developed recurrent FSGS after undergoing renal transplantation. The study was intended to evaluate the long-term outcome of LDL apheresis in patients with FSGS.

The study included the change in lab values (e.g., serum protein, serum albumin, proteinuria) at 1 month after treatment and measured the number of patients achieving remission of nephrotic syndrome at 2 and 5 years after LIPOSORBER® treatment. Although the investigators did not indicate that any of the patients included in the analysis were children, the results can be used to assess effectiveness in children as the course of the disease is sufficiently similar in both adults and children.

The criteria used to assess clinical response were:

- Remission of nephrotic syndrome (NS)
  - o Complete remission
  - Type I incomplete remission: proteinuria negative or < 1.0 g/day and serum albumin > 3.0 g/dL
  - Type II incomplete remission: proteinuria < 3.5 g/day but serum albumin < 3.0 g/dL</li>

## Results

## Effectiveness:

- At 1 month after LDL apheresis total serum protein and albumin increased significantly and proteinuria was significantly decreased.
- Remission of nephrotic syndrome was observed in 18/29 patients followed at 2 years (62%).
- Remission of nephrotic syndrome was observed in 13/15 patients followed at 5 years (86%).

The seven post-transplant patients were included in the 41 patients analyzed at 1 month. The authors did not analyze the data collected from pre- and post-transplant patients separately. Instead, the authors state that the exclusion of the post-transplant patient data did not impact the data trend or significance of the results, indicating that the post-transplant data were similar as a group to the pre-transplant patients in terms of increase in serum protein and albumin and decrease in proteinuria. The authors did not indicate the number of post-transplant patients included in the 2 and 5 years follow-up.

## Safety:

• The incidence of adverse events was not reported.

## Conclusion

The authors conclude that early administration of LDL-apheresis after the onset of nephrotic syndrome associated with FSGS provides a good long-term outcome.

This was a retrospective study. Patients had drug-resistant (persistence of proteinuria ≥ 1.0 g/day after the initial treatment for at least 4 weeks) NS and FSGS. Of the 41 cases of NS due to FSGS, 20 were new-onset. The device treatment was provided in conjunction with standard medications for FSGS/NS: steroids,



cyclosporine A, or other immunosuppressive medications. Each patient received 3-12 treatments with the device.

Adverse events (safety) were not assessed.

In summary, among the 41 patients, encouraging two-year efficacy data were provided for 29 patients (assuming constant enrollment) and five-year data were available for 15 patients. This may be due to steady enrollment throughout the study period.

# Safety Assessment

The studies above did not report reliable adverse event data. However, the safety data from adults with functional hypercholesterolemia (FH) treated with the device can be extrapolated to safety for adults with FSGS treated with the LIPOSORBER® LA-15 System. The table below demonstrates the rates of various adverse events in adults with FH treated with the LIPOSORBER® LA-15 System:

Adverse Event	Episodes		Patients	
Hypotension	41	0.8%	25	33.8%
Nausea/Vomiting	27	0.5%	14	18.9%
Flushing/Blotching	20	0.4%	9	12.2%
Angina/Chest pains	10	0.2%	8	10.8%
Fainting	9	0.2%	6	8.1%
Lightheadedness	7	0.1%	6	8.1%
Anemia	6	0.1%	6	8.1%
Abdominal discomfort	5	0.1%	3	4.1%
Numbness/Tingling	4	0.1%	4	5.4%
Tachycardia	4	0.1%	3	4.1%
Headache	3	0.1%	3	4.1%
Shortness of Breath	3	0.1%	2	2.7%
Hemolysis	3	0.1%	2	2.7%
Bradycardia	3	0.1%	2	2.7%
Itching/Hives	2	0.04%	2	2.7%
Blurred Vision	2	0.04%	2	1.4%

## 2. Pediatrics

Hattori et al. (2003) [13]: This study describes the outcomes of eleven (11) children with steroid resistant primary FSGS who were treated unsuccessfully with conventional-dose cyclosporine therapy and showed persistent nephrotic range proteinuria. At the time of treatment with the LIPOSORBER® LA-15 System, none of the patients had received a renal transplant ("pre-transplant"). At the start of the 7<sup>th</sup> apheresis treatment (average number of treatments: 11.5), prednisone was administered at a dose of 1mg/kg/d for 6 weeks, followed by a tapering schedule during subsequent months.

The effectiveness endpoint was the number of patients achieving remission of nephrotic syndrome. Other measures included renal function (i.e., GFR), degree of proteinuria, cholesterol level and complications of therapy.

The criteria used to assess clinical response were:

- Remission of nephrotic syndrome (NS)
  - Complete remission: reduction in urinary protein (< 4 mg/m²/h) for 3 consecutive days with normal serum albumin and cholesterol levels, and stable renal function
  - o Partial remission: lower urinary protein levels but persistent non-nephrotic proteinuria (protein< 40 mg/m²/h) with normal serum albumin
- Renal Function (as GFR, in ml/min/1.73m²)
- Proteinuria (g/m²/day).

## Results

#### Effectiveness:

- Achievement of remission (defined above) of nephrotic syndrome was observed in 7/11 patients (5 complete and 2 partial).
- Renal function (GFR) for the five (5) patients who achieved complete remission was normal during follow-up (median: 4.4 years, range: 4.0-11.1 years).
- Proteinuria declined in 7/11 patients (as evidenced by remission of nephrotic range proteinuria).

## Safety:

• Only one patient developed a complication (infection of the indwelling catheter used to receive the therapy).

## Conclusion

The authors suggest that combined LDL-apheresis and prednisone therapy can be a valuable therapeutic option for treating patients with steroid resistant FSGS.

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**FSGS** 

# X. ADVERSE EVENTS

Adverse events that may be associated with the use of the LIPOSORBER® LA-15 System in FSGS include, but are not limited to, those listed in the following paragraphs. If a patient experiences an adverse reaction during a procedure, the physician should stop the procedure until the cause of the reaction has been determined and the patient's condition stabilized. The physician should determine all medical responses to adverse reactions based upon the individual patient's physical condition.

- 1) Death
- 2) Cardiac: Various abnormal heart rhythms may develop including bradycardia, tachycardia, and other arrhythmias. Myocardial infarction is another potential adverse cardiac event. If these are detected by vital sign monitoring, physical examination, or electrocardiography, immediate assessment and continued monitoring is essential.
- 3) Thrombocytopenia
- 4) Catheter-related adverse events: Use of the device requires a central venous access (catheter) for children and for some adults given their small venous caliber. Infection of the catheter may occur due to exit site infection, catheter-related bloodstream infection (CRBSI), improper use of the catheter, or internal catheter infection. Aseptic technique is required for catheter use. If an infection or bacteremia is suspected, culture of the catheter ports, in conjunction with peripheral culture (optional), is required. Antibiotic therapy should be provided according to physician discretion. Also, there are other adverse events associated with catheter use (e.g., hemothorax, pneumothorax, blood loss, arterial puncture, superior vena cava syndrome, arrhythmia, central venous stenosis, thrombosis and loss of potential fistula access).
- 5) Hypersensitivity (anaphylactoid) reaction: Use of ACE inhibitors within 24 hours of therapy with the device can cause an increase in bradykinin levels, resulting in severe hypotension. ACE inhibitors should not be taken within 24 hours of therapy with the device.
- 6) Nausea and Vomiting. The procedure should be stopped and the etiology of the nausea and vomiting investigated (e.g., hypotension).
- 7) Reduction in Vitamin E level
- 8) Transient decrease in serum protein and albumin level
- 9) Hypotension: The procedure should be stopped, and the patient should be placed in the Trendelenburg position and/or receive a fluid challenge. If the hypotension persists, the procedure should be terminated. Note: For an "anaphylactoid" reaction, administration of epinephrine, sympathomimetic drugs, prednisolone, antihistamines, and/or calcium have been reported by clinicians as effective interventions.
- 10) Abdominal symptoms. Patients may exhibit nausea, vomiting abdominal discomfort. These events should be addressed with conservative management and supportive care. The procedure should be stopped and the etiology of the nausea and vomiting investigated (e.g., hypotension).



- 11) Flushing/blotching: Check vital signs and reduce the blood flow rate. If symptoms are persistent or repetitive, consider the administration of diphenhydramine (e.g., Benadryl).
- 12) Angina/chest pain: The procedure should be stopped and medical therapy instituted at the discretion of the physician. If the angina persists, the procedure should be terminated.
- 13) Fainting/lightheadedness: See hypotension.
- 14) Anemia: May be minimized by the appropriate use of iron supplements.
- 15) Prolonged bleeding (at cannulation site after removing venous cannulae): Direct manual pressure should be applied until the bleeding stops. If prolonged bleeding occurs (in excess of 20 minutes), adjustment of the heparin dosing may be necessary. It is recommended that, during the subsequent procedure, the heparin dose be reduced and monitored by Activated Clotting Time (ACT). Repetitive LDL apheresis treatment may affect the patient's clotting time. Therefore, a periodic check, of other relevant coagulation parameters is recommended, including the number of thrombocytes and the fibrinogen concentration, in order to ensure that these parameters are sufficient to maintain adequate coagulation.
- 16) Hemolysis: as evidenced by discoloration of plasma or hemolysis as Indicated by activation of the blood leak detector alarm of the MA-03. If either indicator of hemolysis occurs, the procedure should be terminated and the patient's hematocrit, urine output and kidney function monitored.
- 17) Device malfunction: The system contains various components, including LDL adsorption columns (2), plasma separator, tubing system, and an electronic control unit. System malfunction may occur due to any of these components. If system malfunction occurs, the patient's vital signs and clinical status should be monitored immediately and repeatedly. It may be necessary to suspend treatment if the patient develops symptoms or if the problem cannot be readily solved.
- 18) Vertigo
- 19) Diaphoresis
- 20) Urticaria: Mild discomfort may occur requiring supportive care. Vital signs and physical examination of the patient are required in order to assess if urticaria is a component of a more severe, generalized reaction to the therapy. Specific associated symptoms, including, but not limited to, difficulty breathing, chest pain, and dizziness should be addressed by the physician.
- 21) Shivering
- 22) Headaches

# LIPOSORBER® LA-15

# LDL ADSORPTION COLUMNS

Instructions for use in adult and pediatric Focal Segmental Glomerulosclerosis (FSGS)

# FSGS

# **Humanitarian Use Device**

Authorized by Federal (USA) law for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

**Caution:** Federal law restricts this device to sale by or on the order of a physician.

Carefully review the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" and use only under the direction of a licensed physician with appropriate training.

# Kaneka

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# I. Introduction

The LIPOSORBER® LA-15 LDL Adsorption Column set is one of three disposable device components of the LIPOSORBER® LA-15 System. It is comprised of two LIPOSORBER® LA-15 LDL Adsorption Columns, each containing 150 ml of dextran sulfate cellulose adsorbent.

The technical characteristics of the LIPOSORBER® LA-15 LDL Adsorption Columns are explained in Section III of this instructions for use.

Before using the LIPOSORBER® LA-15 LDL Adsorption Column, carefully review this instructions for use and the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" (hereinafter referred to as "Operator's Manual for FSGS").

# II. Indication

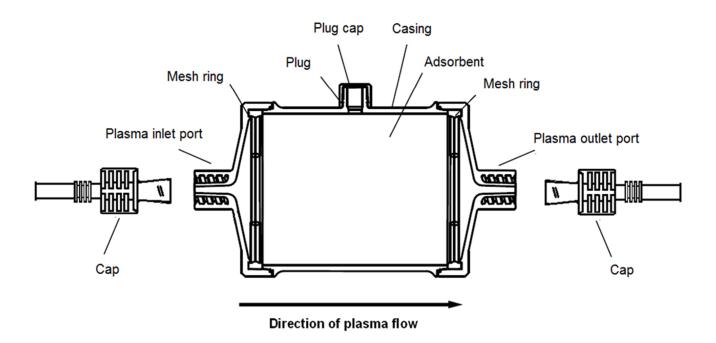
The LIPOSORBER® LA-15 System is indicated for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- standard treatment options, including corticosteroids and/or calcineurin inhibitor, treatments are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.



# **III. Technical Characteristics**

# LIPOSORBER® LA-15 LDL Adsorption Column



	LIPOSORBER® LA-15 LDL Adsorption Column (2 pieces)
Material	Adsorbent: Dextran sulfate cellulose gel (150 mL each) Casing: Polypropylene
Filling Liquid	Sodium citrate/citric acid solution
Sterilization Method	Steam autoclave at 121°C for 20 minutes

# IV. Operations

Carefully review the "Operator's Manual for FSGS" and use only under a physician's direction. **Do not reuse.** 

Use of the LIPOSORBER® LA-15 System in adult and pediatric patients with FSGS is recommended to occur twice weekly for 3 weeks followed by once per week for six weeks.

# V. Contraindications

The LIPOSORBER® LA-15 System must not be used in:

1. patients who have been treated with angiotensin-converting enzyme (ACE) inhibitors within the past 24 hours;

Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER® LA-15 LDL Adsorption Column under concomitant ACE inhibitor medication. The risk of an anaphylactoid reaction may be minimized by withholding the administration of ACE inhibitors for approximately 24 hours before each LDL-apheresis procedure. The time period to withhold ACE inhibitors should be prolonged, if determined by the treating physician, considering each individual's renal function and the biological half-life of the ACE inhibitor currently in use. If required, ACE inhibitor administration may be resumed on the day of the apheresis treatment but only after the apheresis treatment is complete.

- 2. patients for whom adequate anticoagulation cannot be achieved, such as those with severe hemophilia, severe hemorrhage diathesis, severe gastrointestinal ulcers, or who are receiving vitamin K antagonist medications after surgery;
- 3. patients for whom extracorporeal circulation therapy with the LIPOSORBER® LA-15 System cannot be tolerated such as those with severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, acute apoplexy, or severe uncontrollable hypertension or hypotension; and
- 4. patients with hypersensitivity to dextran sulfate cellulose, heparin or ethylene oxide.

# VI. Patient Selection

The following patients may benefit from the LIPOSORBER® LA-15 System. The following are intended only as guidelines for appropriate patient selection:

- Adult and pediatric patients with GFR ≥ 60 ml/min/1.73 m² and a history of primary FSGS accompanied by refractory or recurrent nephrotic syndrome defined as:
  - Patients unresponsive to standard corticosteroid and/or calcineurin inhibitor therapy for at least 8 weeks resulting in failure to achieve complete or partial remission.

or

 Patients intolerant to standard therapies due to severe side effects which negatively affect quality of life without providing an acceptable level of clinical benefit.

or

Patients in whom standard therapies are contraindicated.

OR

 Adult and pediatric post renal transplantation patients with nephrotic syndrome associated with primary FSGS.

# VII. Warnings

- 1. Before using the LIPOSORBER® LA-15 System, including the LIPOSORBER® LA-15 LDL Adsorption Column, carefully review the instructions for use provided for each of the disposables and the "Operator's Manual for FSGS". Persons performing the procedures must be qualified to perform extracorporeal procedures, and have completed the required training program. Users should follow all operating or maintenance procedures published by Kaneka Pharma America LLC and use only the disposable device components recommended by Kaneka Pharma America LLC. Failure to do so may result in injury or loss of life.
- 2. LDL-apheresis treatment of patients who have taken any antihypertensive drugs within 24 hours of treatment may cause hypotension in such patients. When clinically feasible, patients should not receive antihypertensive drugs during the 24-hour period prior to undergoing the LDL-apheresis procedure. Before each treatment, physicians should determine when patients took their last dose of such medication.
- 3. The storage and use of this disposable device other than in accordance with the instructions published by Kaneka Pharma America LLC or the use of disposable device components not recommended by Kaneka Pharma America LLC may result in serious patient injury or loss of life. The manufacturer and distributor(s) of this device will not be responsible for patient safety if the procedures to operate and maintain the LIPOSORBER® LA-15 System are other than those specified in this instructions for use and the Operator's Manual for FSGS.

FSGS

- 4. During an LDL-apheresis procedure, 0.9% Sodium Chloride Injection, USP, 5% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP, and Heparin Sodium Chloride Injection, USP, are used. Carefully identify each solution and ensure that it is properly connected to the LIPOSORBER® LA-15 System. **Using the incorrect solution may result in serious injury or possible death.**
- 5. The LIPOSORBER® LA-15 LDL Adsorption Column is disposable and is **intended for use in a single use only**. **Never reuse**. Discard this disposable after each use.
- 6. The LIPOSORBER® LA-15 System may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended to at all times by a physician or qualified health-care professional adequately trained in all aspects of the procedure.
- 7. Rinsing and subsequent priming of the fluid pathway of the LIPOSORBER® LA-15 LDL Adsorption Columns with appropriate solutions are necessary before commencing the procedure. Because air bubbles in the LDL Adsorption Columns may lead to complications such as coagulation of plasma and impairment of performance, give full attention to measures that will prevent air bubble migration into the columns during rinsing and priming.
- 8. While operating, the differential pressure across the LIPOSORBER® LA-15 LDL Adsorption Column must be **under 100 mmHg**. If the differential pressure across the column rises extremely, the blood flow rate and/or plasma separation rate should be lowered appropriately or even stopped if necessary.
- 9. Citrate preparation (ACD) <u>should never be used</u> as an anticoagulant in the system. The LIPOSORBER® LA-15 System is designed solely for treatment using heparin as an anticoagulant. Anticoagulation is required to prevent thrombus formation from occurring within the extracorporeal circuit. Anticoagulation with too much heparin is associated with an increased risk of bleeding for the patient, especially after the procedure. In order to reduce the risk of bleeding, the puncture sites should be sufficiently compressed so that bleeding is stopped (See Operator's Manual for FSGS at Section <u>1.7 Adverse Events</u>). In some patients the potential for development of a coagulopathy extending several days post-therapy may exist. In addition to adjusting heparin dosage based on clinical observation during and after the apheresis procedure, Activated Clotting Time and/or partial thromboplastin time (PTT) values may be used (See Operator's Manual for FSGS at Section <u>1.9.2 Instructions for Use regarding "Determining Heparin Dosage"</u>).
- 10. To minimize the risk of air embolism, the return tubing line must be connected to the air bubble detector.
- 11. No chemicals or solvents are to be used either inside or outside of this disposable device.
- 12. Due to the risk of reduction of blood pressure with the LIPOSORBER® LA-15 System, extra caution should be exercised in use of the system in patients with systolic and/or diastolic blood pressure  $\leq 5^{th}$  percentile for age, gender and height.
- 13. Use special caution in patients where the extracorporeal volume of approximately 400 ml potentially will exceed 10% of the patient's total blood volume. Such patients are at higher risk of experiencing hypovolemia, which is sometimes followed by hypotension.
- 14. In case of a power failure or system shutdown, terminate the procedure immediately according to the instructions provided in Section <u>7.6 Manual Blood Return</u> of the Operator's Manual for FSGS.



- 15. The safety of LDL-apheresis treatment with the LIPOSORBER® LA-15 System occurring more than twice a week or for treated volumes larger than 60mL/kg patient plasma volumes in FSGS has not been established.
- 16. Do not apply whole blood directly to the LIPOSORBER® LA-15 LDL Adsorption Column. This device is designed for perfusion of plasma only.
- 17. Make sure that the plasma flows in the direction of the arrow on the label of the LIPOSORBER® LA-15 LDL Adsorption Column.

# VIII. Precautions

- 1. The need for the administration of angiotensin receptor blockers (ARBs) prior to the treatment on the day of the apheresis treatment should be determined by the treating physician. If the treating physician determines that it is not necessary, the patient should not take ARBs on the day of the apheresis treatment until the apheresis treatment is completed in order to minimize the risk of a hypotensive reaction during the extracorporeal therapy.
- 2. Medical personnel should monitor the patient for adverse symptoms at all times during treatment and should be trained as to the protocol for responding with appropriate interventions (See Operator's Manual for FSGS at Section <u>1.7 Adverse Events</u>).
- 3. All connections of the extracorporeal circuit should be checked carefully prior to initiating and during the procedure. Avoid unnecessary kinking of the tubing lines and the patient's vascular access devices at all times.
- 4. The transducer protectors must be attached and locked to the machine and tubing lines. Strict aseptic technique should be used during this and all procedures. After the completion of the procedure, properly dispose of all used and unused transducer protectors. Do not reuse.
- 5. Each tubing line must be properly connected and cleared of air, prior to the start of Rinse. Do not allow air to be trapped in the set. Puncturing tubing lines may cause air embolism.
- 6. Drip chambers in the extracorporeal circuit should be kept at least  $\frac{2}{3}$  to  $\frac{3}{4}$  full and monitored at all times in order to decrease the risk of air embolism.
- 7. The fluid circuit of this system is intended to be sterile and nonpyrogenic. Aseptic handling techniques are necessary to maintain these conditions. Prior to use, carefully examine the packaging of the LIPOSORBER® LA-15 Column Set to ensure that it is intact and undamaged. Do not use the LIPOSORBER® LA-15 LDL Adsorption Column if the package, sterile bag, protective cap or the product itself is not intact or is damaged. Do not open the bags containing the LIPOSORBER® LA-15 LDL Adsorption Column until immediately prior to use.
- 8. The safety and probable benefit of LDL-apheresis using the LIPOSORBER® LA-15 System in FSGS have not been established for: (1) patients less than 21 kg in body weight; (2) patients less than 5 years of age; (3) patients with certain cardiac impairments such as uncontrolled arrhythmia, unstable angina, decompensated congestive heart failure or valvular disease; and (4) patients with thyroid disease or liver abnormalities.
- 9. The safety and probable benefit of LDL-apheresis using the LIPOSORBER® LA-15 System in FSGS has not been established for pregnant women or for women during the lactation period, e.g. the effect of treatments on folic acid levels has not been determined.



- 10. Closely monitor patient clotting time periodically during the procedure to ensure that an adequate level of anticoagulation is maintained.
- 11. Instructions for heparin administration should be followed as stated in the guidance provided by the manufacturer in the Operator's Manual for FSGS. The amounts of heparin outlined in the Operator's Manual for FSGS are intended as general suggestions. The exact amount, frequency and method of administration of heparin are the sole responsibility of the prescribing/attending physician and should be selected based on the individual patient's clinical condition.
- 12. Physicians and operators should follow the OSHA and the CDC/ACIP Adult Immunization Guidelines for Hemodialysis Patients. It is recommended that patients be screened for Hepatitis B and other infectious diseases; however, due to possible exposure to hepatitis virus, human immunodeficiency virus, and other infectious agents when handling extracorporeal blood circuits, blood or blood products, universal precautions should be taken at all times to prevent the exposure to and transmission of such agents.
- 13. When disposing of the disposable device components and wastes, comply with all local requirements and the policies of the facility regarding precautions for and prevention of infection and environmental pollution.
- 14. In transporting and storing the disposable, handle with care. Store the disposable in a clean and secure area at room temperature (5-30°C), avoiding exposure to direct sunlight, high humidity or excessive vibration. Handle the LIPOSORBER® LA-15 LDL Adsorption Column with care to avoid dropping or other sudden impacts and never allow it to freeze. Do not use an LDL Adsorption Column that may have been dropped, damaged or frozen.
- 15. The expiration date of the LIPOSORBER® LA-15 column is 4 years from the sterilization date. The LIPOSORBER® LA-15 column must never be used after the expiration date.
- 16. The LIPOSORBER® LA-15 System includes a blood warmer with a temperature setting range of 35-40 °C. It is recommended that the blood warmer be set at a temperature between 36-38 °C in order to avoid significant decreases in blood temperature during extracorporeal circulation.
- 17. Anemia may be minimized by the appropriate use of iron supplements.

# IX. Clinical Data

Clinical data to support the safety and probable benefit of LIPOSORBER® LA-15 System for FSGS can be divided to pre-transplant FSGS and post-transplant FSGS.

# 1. Adults

Published Clinical Studies of LIPOSORBER® LA-15 System Treatment for Patients with Nephrotic Syndrome (NS) and FSGS in adults are summarized in the table below.

Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre- transplant or Post- transplant
Muso 2015 [1] Muso 2015 [2]	44 (26 with FSGS)	Prospective Multicenter Single arm	Immediate to 2 years after treatment	Urinary Protein (UP) decreased from 6.28 ± 2.96 to 3.46 ± 3.34 g/day.  21/44 patients (48%) had a favorable 2-years outcome.	Pre- transplant
Muso 2001 [3] Muso 1999 [4]	17 (14 with FSGS)	Prospective Multicenter Controlled	Immediate to 2 years after treatment	UP decreased from 6.2 ± 3.3 to 2.7 ± 2.7 g/day.  The rate of achieving complete or incomplete remission was 71%.  As for the 2-years outcomes, 13/17 patients (76%) maintained UP <1.0 g/day.	Pre- transplant
Yokoyama 2002 [5]	6 (2 with FSGS; 1 treated with LIPOSO RBER®)	Prospective Single Center	Unknown	This was a prospective study of the effects of lymphocytapheresis in treating various forms of NS in 6 patients. One patient with FSGS failed to respond to one month of LIPOSORBER® treatment.	Pre- transplant
Nakamura 2006 [6]	8 FSGS	Prospective Single Center	2 weeks	UP decreased from 8.8 ± 4.2 g/day to 2.0 ± 1.2 g/day.	Pre- transplant
Muso 2007 [7]	41 FSGS	Retrospectiv e	5 years	At 1 month after LDL apheresis UP was significantly decreased.  Remission of nephrotic syndrome was observed in 18/29 patients (62%) followed at 2 years and 13/15 patients (86%) followed at 5 years.	Pre- transplant and Post- transplant



Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre- transplant or Post- transplant			
Case Studie	Case Studies							
Masutani 2005 [8]	1 FSGS	Case Report	1 year	LIPOSORBER® in conjunction with drug treatment resulted in reduction of UP from 6.8 g/day to 2.0 g/day.  Incomplete remission had been maintained for more than 1 year.	Post- transplant			
Miura 2009 [9]	1 FSGS	Case Report	40 days	Six cycles of hemodialysis were performed in conjunction with 4 cycles of LIPOSORBER® treatment. UP and serum creatinine levels recovered to normal values, and UP became undetectable by 40 days post-treatment.	Pre- transplant			
Miyazono 2008 [10]	1 FSGS	Case Report	Unknown	After 6 treatment sessions, the patient's UP decreased to non-nephrotic level. Furthermore, the patient's hypoproteinemia improved and renal function returned to normal. Although the patient experienced a relapse of nephrotic syndrome, 6 more sessions of LIPOSORBER® treatment brought the UP down to 0.8 g/day.	Pre- transplant			
Tsukada 2006 [11]	1 FSGS	Case Report	Unknown	The patient underwent 8 sessions of treatment using LIPOSORBER®, which resulted in the reduction of the UP level and improvement of renal functions.	Post- transplant			
Haikal 2016 [12]	1 FSGS	Case Report	5 months	Partial remission sustained 5 months post therapy	Pre- transplant			

- 1) Pre-transplant FSGS
- (i) Muso et al. (2001) [3]: This study describes the comparison of efficacy between the treatment with the LIPOSORBER® LA-15 System in combination with steroids (LDL-A group) and that with steroids only (steroid monotherapy (SM) group) for patients with nephrotic syndrome who did not respond to full-dose (prednisolone, daily 1 mg/kg b.w.) therapy of 1-month duration under the fixed treatment protocol. The LDL group consisted of 17 patients (FSGS: 14, minimal change nephrotic syndrome (MCNS): 3) who were treated with the LIPOSORBER® LA-15 System. Treatments were performed twice a week for 3 weeks followed by weekly treatment for 6 weeks. The SM group included 10 patients (FSGS: 9, MCNS: 1) who were treated only with continuous full-dose steroids.

## Results

## Effectiveness:

- Total cholesterol (TC) level in the LDL-A group was significantly decreased after the treatment (337±118 to 242±45.2 mg/dL, p=0.006), whereas decrease of TC level in the SM group was not significant (448±106 to 366±159 mg/dL, p=0.169).
- Hypoalbuminemia significantly improved in the LDL-A group (2.7±0.7 to 3.1±0.7 g/dL, p=0.014), while almost no change was noted in the SM group (2.8±0.4 to 2.9±0.7 g/dL, p=0.822).
- Proteinuria was significantly ameliorated in the LDL-A group (6.2±3.3 to 2.7±2.7 g/day, p=0.0008), while significant amelioration of proteinuria was not observed in the SM group (8.7±4.0 to 8.2±7.7 g/day, p=0.85).
- Average duration needed for a decrease of urinary protein to <3.5 g/day was significantly shorter in the LDL group than in the SM group (14.7±19.6 days vs 47.8±6.9 days, p=0.002).
- At the end of the treatment period, 9 patients (52%) in the LDL-A group achieved urinary protein level <1.0 g/day, whereas only 1 patient (10%) showed the same level in the SM group.
- As for the long-term outcomes (2 years after the end of the treatment period),
   13 out of 17 patients (76%) maintained urinary protein level <1.0 g/day in the LDL-A group, compared to only 2 in 9 patients (22%) in the SM group.</li>

## Safety:

The incidence of adverse events was not reported.

## Conclusion

Superiority of therapeutic efficacy of the treatment with the LIPOSORBER® LA-15 System in combination with steroids to that with steroids alone was demonstrated in controlled study.

This study was a follow-up of the multicenter study reported by Muso et al (Kidney Int) in 1999. In this study, the authors did not report any adverse events.

Summary: Among the 17 patients with FSGS, short-term and medium-term efficacy data were provided compared to controls. Adverse events were not mentioned in the report.



(ii) Nakamura et al. (2006) [6]: This study investigated the effect of LIPOSORBER® LA-15 System in treating FSGS as part of a larger study to determine whether the levels of urinary liver-type fatty acid-binding protein (L-FABP) are associated with the severity of nephrotic syndrome. At the beginning of the study, all FSGS patients received 60 mg/day prednisone for 6 months, followed by either cyclophosphamide or mizoribine for another 6 months. Treatment with LIPOSORBER® LA-15 System was performed in 8 patients with drug-resistant FSGS twice a week for 3 weeks, then once a week for 6 weeks. In each 3-hour treatment session, 3000-4000 mL of plasma were treated. Renal function in terms of daily urinary protein excretion and serum creatinine levels were measured before the start of treatment and 2 weeks after the final treatment session.

## Results

## Effectiveness:

- Comparing the clinical parameters before and after the treatment, urinary protein and serum creatinine decreased significantly from 8.8 ± 4.2 g/day to 2.0 ± 1.2 g/day (p < 0.01) and from 123.8 ± 26.5 µmol/L to 97.2 ± 17.7 µmol/L (p < 0.05), respectively, and total protein increased from 40 ± 8 g/L to 60 ± 9 g/L (p < 0.01).</li>
- In addition, serum level of L-FABP decreased from 122.6  $\pm$  78.4  $\mu$ g/gCr to 64.4  $\pm$  43.8  $\mu$ g/gCr (p < 0.05).

# Safety:

 The article did not report any adverse events associated with LIPOSORBER<sup>®</sup> LA-15 System.

## Conclusion

This study demonstrated that LDL apheresis therapy with LIPOSORBER® LA-15 System ameliorated proteinuria, hypoproteinemia, and renal function in drug-resistant FSGS.

This was a prospective study. Among the 8 patients with FSGS, encouraging short-term efficacy data were provided. A control arm was not included in this study. Adverse events were not mentioned in the report.

(iii) Muso et al. (2015) [1]: The investigators conducted a prospective, observational, multi-center cohort study (POLARIS study). In the POLARIS study, patients with nephrotic syndrome who did not respond to primary medication were registered before starting the treatment with LIPOSORBER® LA-15 System and clinical effectiveness and safety were examined. A total of 58 patients (who underwent 64 treatments) were registered in the study. Of the 64 treatment regimens, 17 were excluded for various reasons, leaving 47 treatment regimens for 44 patients available for analysis. As for FSGS, 23 patients were registered and underwent a total of 26 treatments. Clinical data were collected at baseline and after treatment with LDL-apheresis based on 24-hour urinalysis. Lipid profiles and clinical parameters were compared between before and after the treatment.

## Results

#### Effectiveness:

- TC and LDL cholesterol (LDL-C) levels were significantly decreased after the treatment (331.10 ± 113.25 to 210.38 ± 77.4 mg/dL; p<0.01, 205.86 ± 100.to 84 92.37 ± 56.64 mg/dL; p<0.01, respectively), whereas the changes of triglyceride (TG) and HDL-cholesterol (HDL-C) were not significant (262.74 ± 155.17 to 241.30 ± 182.14 mg/dL; n.s., 69.49 ± 22.58 to 73.64 ± 23.40 mg/dL; n.s.).</li>
- Hypoproteinemia (serum protein), hypoalbuminemia (serum albumin), and proteinuria (urinary protein) were significantly ameliorated immediately after treatment (4.42 ± 0.69 to 4.68 ± 0.81 g/dL; p<0.05, 2.15 ± 0.63 to 2.63 ± 0.79 g/dL; p<0.01, and 6.28 ± 2.96 to 3.46 ± 3.34 g/day; p<0.01, respectively). In addition, renal function (creatinine clearance) significantly improved immediately after treatment (58.59 ± 41.35 to 65.11 ± 41.39 mL/min; p<0.05).</li>
- Serum levels of fibrinogen and thrombin-antithrombin III complex (TAT) level were significantly reduced (374.46 ± 130.04 to 297.92 ± 108.87 mg/dL; p<0.01, 16.39 ± 33.60 to 12.21 ± 34.10 ng/mL; p<0.05, respectively) suggesting that treatment with LIPOSORBER® LA-15 System exerts anticoagulation activity.</li>

## Safety:

The incidence of adverse events was not reported.

## Conclusion

LDL apheresis therapy with LIPOSORBER® LA-15 System rapidly ameliorated symptoms of nephrotic syndrome i. e. proteinuria and hypoproteinemia in more than half of the patients who failed to respond to primary medication.

This was a short-term study.

The endpoints were:

- Complete remission: Urinary Protein (UP) = undetectable
- Incomplete Remission I: UP < 1.0g/day</li>
- Incomplete Remission II: 1.0 g ≤ UP < 3.5 g/day
- No effect: UP ≥ 3.5 g/day

In this study, complete or incomplete remission were considered favorable outcomes.

The average number of apheresis sessions was 9.6/patient. An average of 3.5 L of plasma was treated per session. Among the 44 patients, FSGS was the diagnosis in 23 (52.3%) of the patients.



(iv) Muso et al. (2015) [2]: The long-term (2 years) outcome of the POLARIS cohort was investigated for the 44 subjects. Of the 58 patients who were registered in the POLARIS study, 5 were excluded from the study because of protocol violation or inadequate data collection, 6 were lost to follow up, and 3 died during the follow-up period, thus leaving 44 subjects eligible for analysis at two years. As for primary diseases of the subjects, FSGS was found in the majority of cases, presenting in 28 subjects (63.6%).

## Results

## Effectiveness:

- Twenty-one (21) of the 44 subjects (47.7%) had a favorable outcome, with 11 subjects (25%) in complete remission (defined as urinary protein undetectable) and 10 subjects (22.7%) in incomplete remission I (defined as urinary protein level < 1.0 g/day). Twenty-three (23) subjects (52.3%) had an unfavorable result, with 11 (25%) in incomplete remission II (defined as 1.0 g/day ≤ urinary protein < 3.5 g/day) and 12 (27.3%) with no effect (defined as urinary protein level ≥ 3.5/day).</p>
- An analysis was performed of the factors affecting outcome. The authors found that the urinary protein level post-treatment was strongly associated with 2-year outcome (p < 0.001). For subjects with favorable outcomes, the urinary level after treatment was 1.68 ± 1.76 g/day compared to 6.18 ± 3.24 g/day for subjects with unfavorable outcomes.
- Improvement of parameters representing disease conditions of nephrotic syndrome, including serum albumin, eGFR, urinary protein and total and LDL cholesterol were all significantly associated with favorable outcome. This suggests that an early rapid alleviation of nephrotic syndrome by LDL-apheresis contributes to a favorable outcome.

## Safetv:

 No adverse event associated with LIPOSORBER® LA-15 System was reported in this report.

## Conclusion

The POLARIS study demonstrated that LDL apheresis therapy with LIPOSORBER® LA-15 System ameliorates nephrotic conditions and that the therapeutic efficacy of LDL apheresis was largely maintained for two years.

During the time from the short- to long-term POLARIS study, 3 subjects died of diseases unrelated to NS (cerebral infarction, lung cancer and pneumonia). Given the variety of histological diagnoses in the patients included in the study, it was challenging to ascertain the outcomes for patients with FSGS versus those with other diseases. That said, the study does report that urine protein levels decreased significantly and similarly for patients with/without FSGS and this study provides reasonable assurance of efficacy of the device in about 50% of patients with FSGS.

# 2) Post-transplant FSGS

<u>Muso et al. (2007) [7]:</u> This study describes 41 patients with refractory FSGS. The study population included a sub-set of 7 patients who developed recurrent FSGS after undergoing renal transplantation. The study was intended to evaluate the long-term outcome of LDL apheresis in patients with FSGS.

The study included the change in lab values (e.g., serum protein, serum albumin, proteinuria) at 1 month after treatment and measured the number of patients achieving remission of nephrotic syndrome at 2 and 5 years after LIPOSORBER® treatment. Although the investigators did not indicate that any of the patients included in the analysis were children, the results can be used to assess effectiveness in children as the course of the disease is sufficiently similar in both adults and children.

The criteria used to assess clinical response were:

- Remission of nephrotic syndrome (NS)
  - o Complete remission
  - Type I incomplete remission: proteinuria negative or < 1.0 g/day and serum albumin > 3.0 g/dL
  - Type II incomplete remission: proteinuria < 3.5 g/day but serum albumin < 3.0 g/dL</li>

## Results

## Effectiveness:

- At 1 month after LDL apheresis total serum protein and albumin increased significantly and proteinuria was significantly decreased.
- Remission of nephrotic syndrome was observed in 18/29 patients followed at 2 years (62%).
- Remission of nephrotic syndrome was observed in 13/15 patients followed at 5 years (86%).

The seven post-transplant patients were included in the 41 patients analyzed at 1 month. The authors did not analyze the data collected from pre- and post-transplant patients separately. Instead, the authors state that the exclusion of the post-transplant patient data did not impact the data trend or significance of the results, indicating that the post-transplant data were similar as a group to the pre-transplant patients in terms of increase in serum protein and albumin and decrease in proteinuria. The authors did not indicate the number of post-transplant patients included in the 2 and 5 years follow-up.

## Safety:

• The incidence of adverse events was not reported.

## Conclusion

The authors conclude that early administration of LDL-apheresis after the onset of nephrotic syndrome associated with FSGS provides a good long-term outcome.

This was a retrospective study. Patients had drug-resistant (persistence of proteinuria ≥ 1.0 g/day after the initial treatment for at least 4 weeks) NS and FSGS. Of the 41 cases of NS due to FSGS, 20 were new-onset. The device treatment was provided in conjunction with standard medications for FSGS/NS: steroids,



cyclosporine A, or other immunosuppressive medications. Each patient received 3-12 treatments with the device.

Adverse events (safety) were not assessed.

In summary, among the 41 patients, encouraging two-year efficacy data were provided for 29 patients (assuming constant enrollment) and five-year data were available for 15 patients. This may be due to steady enrollment throughout the study period.

# Safety Assessment

The studies above did not report reliable adverse event data. However, the safety data from adults with functional hypercholesterolemia (FH) treated with the device can be extrapolated to safety for adults with FSGS treated with the LIPOSORBER® LA-15 System. The table below demonstrates the rates of various adverse events in adults with FH treated with the LIPOSORBER® LA-15 System:

Adverse Event	Episodes		Patients	
Hypotension	41	0.8%	25	33.8%
Nausea/Vomiting	27	0.5%	14	18.9%
Flushing/Blotching	20	0.4%	9	12.2%
Angina/Chest pains	10	0.2%	8	10.8%
Fainting	9	0.2%	6	8.1%
Lightheadedness	7	0.1%	6	8.1%
Anemia	6	0.1%	6	8.1%
Abdominal discomfort	5	0.1%	3	4.1%
Numbness/Tingling	4	0.1%	4	5.4%
Tachycardia	4	0.1%	3	4.1%
Headache	3	0.1%	3	4.1%
Shortness of Breath	3	0.1%	2	2.7%
Hemolysis	3	0.1%	2	2.7%
Bradycardia	3	0.1%	2	2.7%
Itching/Hives	2	0.04%	2	2.7%
Blurred Vision	2	0.04%	2	1.4%

#### 2. Pediatrics

Hattori et al. (2003) [13]: This study describes the outcomes of eleven (11) children with steroid resistant primary FSGS who were treated unsuccessfully with conventional-dose cyclosporine therapy and showed persistent nephrotic range proteinuria. At the time of treatment with the LIPOSORBER® LA-15 System, none of the patients had received a renal transplant ("pre-transplant"). At the start of the 7<sup>th</sup> apheresis treatment (average number of treatments: 11.5), prednisone was administered at a dose of 1mg/kg/d for 6 weeks, followed by a tapering schedule during subsequent months.

The effectiveness endpoint was the number of patients achieving remission of nephrotic syndrome. Other measures included renal function (i.e., GFR), degree of proteinuria, cholesterol level and complications of therapy.

The criteria used to assess clinical response were:

- Remission of nephrotic syndrome (NS)
  - Complete remission: reduction in urinary protein (< 4 mg/m²/h) for 3 consecutive days with normal serum albumin and cholesterol levels, and stable renal function
  - o Partial remission: lower urinary protein levels but persistent non-nephrotic proteinuria (protein< 40 mg/m²/h) with normal serum albumin
- Renal Function (as GFR, in ml/min/1.73m²)
- Proteinuria (g/m²/day).

#### Results

#### Effectiveness:

- Achievement of remission (defined above) of nephrotic syndrome was observed in 7/11 patients (5 complete and 2 partial).
- Renal function (GFR) for the five (5) patients who achieved complete remission was normal during follow-up (median: 4.4 years, range: 4.0-11.1 years).
- Proteinuria declined in 7/11 patients (as evidenced by remission of nephrotic range proteinuria).

#### Safety:

• Only one patient developed a complication (infection of the indwelling catheter used to receive the therapy).

#### Conclusion

The authors suggest that combined LDL-apheresis and prednisone therapy can be a valuable therapeutic option for treating patients with steroid resistant FSGS.

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**FSGS** 

#### X. ADVERSE EVENTS

Adverse events that may be associated with the use of the LIPOSORBER® LA-15 System in FSGS include, but are not limited to, those listed in the following paragraphs. If a patient experiences an adverse reaction during a procedure, the physician should stop the procedure until the cause of the reaction has been determined and the patient's condition stabilized. The physician should determine all medical responses to adverse reactions based upon the individual patient's physical condition.

- 1) Death
- 2) Cardiac: Various abnormal heart rhythms may develop including bradycardia, tachycardia, and other arrhythmias. Myocardial infarction is another potential adverse cardiac event. If these are detected by vital sign monitoring, physical examination, or electrocardiography, immediate assessment and continued monitoring is essential.
- 3) Thrombocytopenia
- 4) Catheter-related adverse events: Use of the device requires a central venous access (catheter) for children and for some adults given their small venous caliber. Infection of the catheter may occur due to exit site infection, catheter-related bloodstream infection (CRBSI), improper use of the catheter, or internal catheter infection. Aseptic technique is required for catheter use. If an infection or bacteremia is suspected, culture of the catheter ports, in conjunction with peripheral culture (optional), is required. Antibiotic therapy should be provided according to physician discretion. Also, there are other adverse events associated with catheter use (e.g., hemothorax, pneumothorax, blood loss, arterial puncture, superior vena cava syndrome, arrhythmia, central venous stenosis, thrombosis and loss of potential fistula access).
- 5) Hypersensitivity (anaphylactoid) reaction: Use of ACE inhibitors within 24 hours of therapy with the device can cause an increase in bradykinin levels, resulting in severe hypotension. ACE inhibitors should not be taken within 24 hours of therapy with the device.
- 6) Nausea and Vomiting. The procedure should be stopped and the etiology of the nausea and vomiting investigated (e.g., hypotension).
- 7) Reduction in Vitamin E level
- 8) Transient decrease in serum protein and albumin level
- 9) Hypotension: The procedure should be stopped, and the patient should be placed in the Trendelenburg position and/or receive a fluid challenge. If the hypotension persists, the procedure should be terminated. Note: For an "anaphylactoid" reaction, administration of epinephrine, sympathomimetic drugs, prednisolone, antihistamines, and/or calcium have been reported by clinicians as effective interventions.
- 10) Abdominal symptoms. Patients may exhibit nausea, vomiting abdominal discomfort. These events should be addressed with conservative management and supportive care. The procedure should be stopped and the etiology of the nausea and vomiting investigated (e.g., hypotension).



- 11) Flushing/blotching: Check vital signs and reduce the blood flow rate. If symptoms are persistent or repetitive, consider the administration of diphenhydramine (e.g., Benadryl).
- 12) Angina/chest pain: The procedure should be stopped and medical therapy instituted at the discretion of the physician. If the angina persists, the procedure should be terminated.
- 13) Fainting/lightheadedness: See hypotension.
- 14) Anemia: May be minimized by the appropriate use of iron supplements.
- 15) Prolonged bleeding (at cannulation site after removing venous cannulae): Direct manual pressure should be applied until the bleeding stops. If prolonged bleeding occurs (in excess of 20 minutes), adjustment of the heparin dosing may be necessary. It is recommended that, during the subsequent procedure, the heparin dose be reduced and monitored by Activated Clotting Time (ACT). Repetitive LDL apheresis treatment may affect the patient's clotting time. Therefore, a periodic check, of other relevant coagulation parameters is recommended, including the number of thrombocytes and the fibrinogen concentration, in order to ensure that these parameters are sufficient to maintain adequate coagulation.
- 16) Hemolysis: as evidenced by discoloration of plasma or hemolysis as Indicated by activation of the blood leak detector alarm of the MA-03. If either indicator of hemolysis occurs, the procedure should be terminated and the patient's hematocrit, urine output and kidney function monitored.
- 17) Device malfunction: The system contains various components, including LDL adsorption columns (2), plasma separator, tubing system, and an electronic control unit. System malfunction may occur due to any of these components. If system malfunction occurs, the patient's vital signs and clinical status should be monitored immediately and repeatedly. It may be necessary to suspend treatment if the patient develops symptoms or if the problem cannot be readily solved.
- 18) Vertigo
- 19) Diaphoresis
- 20) Urticaria: Mild discomfort may occur requiring supportive care. Vital signs and physical examination of the patient are required in order to assess if urticaria is a component of a more severe, generalized reaction to the therapy. Specific associated symptoms, including, but not limited to, difficulty breathing, chest pain, and dizziness should be addressed by the physician.
- 21) Shivering
- 22) Headaches

# LIPOSORBER® LA-15 SYSTEM

# Operator's manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)

#### **Humanitarian Use Device**

Authorized by Federal (USA) law for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

**Caution:** Federal law restricts this device to sale by or on the order of a physician.

# Important:

Be sure to carefully read this operator's manual before use.

Keep this manual by the machine for immediate reference.

This manual is applicable to the KANEKA MA-03 with the software version 1.2.

The software version is displayed on the KANEKA MA-03's screen.

KANEKA PHARMA AMERICA LLC NEW YORK, NY

# **FOREWORD**

ABOUT THE LIPOSORBER® LA-15 SYSTEM OPERATOR'S MANUAL



This manual is applicable to the KANEKA MA-03 with the software version 1.2.

Confirm that the model of the machine and the software version described in this manual correspond to those in the machine to be used.

- 1. The model of the machine is described in the rating plate on the rear panel.
- 2. The software version is displayed on the LCD screen of the operation panel.

Maintenance mode menu screen is displayed on the LCD screen by touching the Maintenance mode key in the bottom area of the LCD screen.

Machine information screen opens by touching the Machine information key, and the software version is displayed on the LCD screen.

This Operator's Manual contains the information needed to operate the LIPOSORBER® LA-15 System correctly and safely. It is essential that you read this manual carefully and be sure you understand it before you operate the LIPOSORBER® LA-15 System. Pay particular attention to the Cautions and Warnings and to the items indicated by the safety alert symbol ...

#### • COMMENTS OR QUESTIONS

All reasonable efforts have been made to assure the accuracy of the contents of this Operator's Manual. If you have any comments or questions regarding this manual or any questions that are not answered in this manual, contact Kaneka Pharma America LLC.

Kaneka Pharma America LLC 546 Fifth Avenue; 21st Floor New York, NY 10036

Telephone: (212) 705-4340 Fax: (212) 705-4350

#### ABOUT THE SAFETY ALERT SYMBOL

The safety alert symbol  $\triangle$  identifies situations that could be dangerous to the operator or the patient and directs your attention to the proper operation of the Apheresis Machine KANEKA MA-03 (hereinafter the MA-03). Read and understand each Warning, Caution and Notice thoroughly. See the next page of this manual for an explanation of these safety alerts.

This manual is copyrighted by Kaneka Pharma America LLC and no part of it should be reprinted without Kaneka Pharma America LLC's prior permission.

This operator's manual is intended to be a reference for proper and safe operation of the MA-03. In no way is this manual intended to be a step-by-step guide in the actual decisions regarding the treatment of the patients.

For proper and safe operation, be sure to carefully read this operator's manual before use. Keep this manual by the machine for immediate reference.

# Symbols and Remarks for Safety

In this manual and on each MA-03, the following safety symbols and remarks are shown for safe and proper use of the equipment.

The meanings of the symbols are as follows.

Familiarize yourself with the meanings of the symbols before reading the text of the manual.



DANGER indicates an imminently hazardous situation which, if not avoided, will result in death or serious injury.



WARNING indicates a potentially hazardous situation which, if not avoided, may result in death or serious injury.



CAUTION indicates a potentially hazardous situation which, if not avoided, may result in minor or slightly injury.



NOTICE indicates practices you must know when operating the machine, although the situation may not be as serious as those mentioned above.

#### • COMPONENTS

The LIPOSORBER® LA-15 System is an integrated, automated extracorporeal blood processing system that includes the following 3 disposables and a control/monitor machine:

LIPOSORBER® LA-15 LDL Adsorption Column set (disposable) consisting of two columns, each containing 150 ml of dextran sulfate cellulose adsorbent;

SULFLUX® KP-05 Plasma Separator (disposable) containing hollow fibers made of polyethylene coated by an ethylene-vinyl alcohol copolymer;

Tubing System for Plasmapheresis (NK-M3R(U)) (disposable); and

the Apheresis Machine KANEKA MA-03, which monitors and controls the LDL-apheresis procedure.

#### • PRINCIPLES OF OPERATION

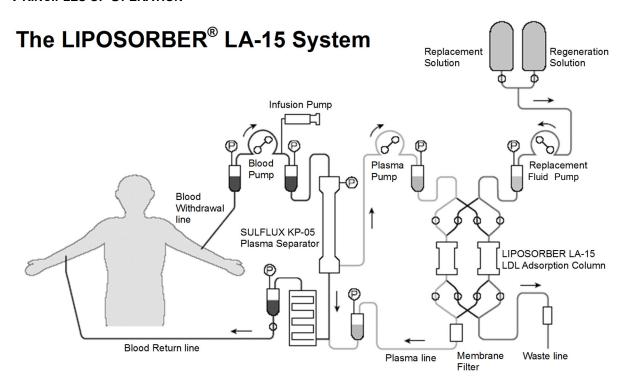


Figure A. LIPOSORBER® LA-15 System overview.

As illustrated in Figure A, the patient's blood is withdrawn via a venous access connected to the blood withdrawal line and enters the plasma separator. As blood flows into the top of the separator, through the hollow fibers, plasma is separated and exits from the separator side outlet. The remaining blood, including red and white blood cells and platelets, exits from the separator bottom outlet. The cell-free plasma enters the top inlet of one of the two LDL adsorption columns. As the plasma passes through the column, the apolipoprotein B-containing lipoproteins - LDL, VLDL, and Lp(a) - are selectively adsorbed in the column. There is minimal effect on HDL and other plasma components. The LDL-depleted plasma exits the adsorption column bottom outlet, flows through the membrane filter, is recombined with the blood cells exiting the separator bottom outlet and is returned to the patient via venous access.

When the first 500 ml of plasma has been treated with the left column, the MA-03 automatically switches the plasma flow to the right column. At this point, the plasma exiting the plasma separator flows into the right column, while the plasma remaining in the left column is pushed out with 140 ml of replacement solution (Lactated Ringer's Injection, USP) and returned to the patient.

When recovery of the plasma from the left column is completed, the plasma return line is switched over from the left column to the right column, enabling the plasma in the right column to return to the patient. Throughout this column switch-over operation, the replacement fluid pump is automatically operated at the same speed as the plasma pump. The replacement solution during each switch-over is not returned to the patient.

While the right column is still treating plasma, the left column is rinsed with 105 ml of regeneration solution (5% Sodium Chloride Injection, USP), and its original adsorption capacity is restored. Along with the regeneration solution, apolipoprotein B-containing lipoproteins LDL, VLDL, and Lp(a) are flushed from the column through the waste line into the waste bag. When elution is completed, 355 ml of replacement solution is pumped through the column to rinse out the regeneration solution completely and re-prime the column. The column is now ready for the next cycle of adsorption.

Subsequent switch-over and regeneration cycles are repeated every time 600 ml of plasma has been treated by one of the two LDL adsorption columns, allowing continuous LDL-apheresis until the predetermined plasma volume has been treated. The first switch-over occurs at 500 ml because initial levels of LDL, VLDL, and Lp(a) are higher in the first cycle.

The tubing system, plasma separator and two LDL adsorption columns, are intended for single use only. All disposables must be discarded after each procedure.

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# **APPENDIX A**

Abbreviations and Symbols of the MA-03

# 1. INTRODUCTION

This operator's manual is intended to be a reference for proper and safe operation of the Apheresis Machine Kaneka MA-03. In no way is this manual intended to be a step-by-step guide in the actual decisions regarding the treatment of the patients.

For proper and safe operation, be sure to carefully read this operator's manual before use. Keep this manual by the machine for immediate reference.

# 1.1 Description

The LIPOSORBER® LA-15 System is an integrated, automated extracorporeal blood processing system that includes the following 3 disposables and a control/monitor machine:

LIPOSORBER® LA-15 LDL Adsorption Column set (disposable) consisting of two columns, each containing 150 ml of dextran sulfate cellulose adsorbent;

SULFLUX® KP-05 Plasma Separator (disposable) containing hollow fibers made of polyethylene coated by an ethylene-vinyl alcohol copolymer;

Tubing System for Plasmapheresis (NK-M3R(U)) (disposable); and

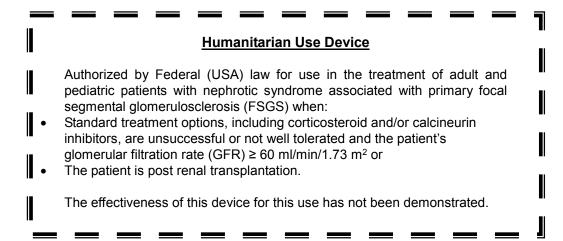
the Apheresis Machine KANEKA MA-03, which monitors and controls the LDL-apheresis procedure.

All of the above components are authorized by Federal law for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS).

#### Caution: Federal law restricts this device to sale by or on the order of a physician.

This system may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended at all times by a physician or qualified health-care professional adequately trained in all aspects of the procedure. All physicians and medical personnel utilizing the LIPOSORBER® LA-15 System will be required to have completed an appropriate training program.

# 1.2 Indications for Use



The LIPOSORBER® LA-15 System is indicated for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis when:

- Standard treatment options, including corticosteroids and/or calcineurin inhibitor treatments, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

# 1.3 Contraindications

The LIPOSORBER® LA-15 System must not be used in:

- 1. patients who have been treated with angiotensin-converting enzyme (ACE) inhibitors within the past 24 hours;
  - Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER® LA-15 LDL Adsorption Column under concomitant ACE inhibitor medication. The risk of an anaphylactoid reaction may be minimized by withholding the administration of ACE inhibitors for approximately 24 hours before each LDL-apheresis procedure. The time period to withhold ACE inhibitors should be prolonged, if determined by the treating physician, considering each individual's renal function and the biological half-life of the ACE inhibitor currently in use. If required, ACE inhibitor administration may be resumed on the day of the apheresis treatment but only after the apheresis treatment is complete.
- 2. patients for whom adequate anticoagulation cannot be achieved, such as those with severe hemophilia, severe hemorrhage diathesis, severe gastrointestinal ulcers, or who are receiving vitamin K antagonist medications after surgery;
- 3. patients for whom extracorporeal circulation therapy with the LIPOSORBER <sup>®</sup> LA-15 System cannot be tolerated such as those with severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, acute apoplexy, or severe uncontrollable hypertension or hypotension; and
- 4. patients with hypersensitivity to dextran sulfate cellulose, heparin or ethylene oxide.

## 1.4 Patient Selection

The following patients may benefit from the LIPOSORBER® LA-15 System. The following are intended only as guidelines for appropriate patient selection:

- Adult and pediatric patients with GFR > 60 ml/min/1.73 m<sup>2</sup> and a history of primary FSGS accompanied by refractory or recurrent nephrotic syndrome defined as:
  - Patients unresponsive to standard corticosteroid and/or calcineurin inhibitor therapy for at least 8 weeks resulting in failure to achieve complete or partial remission

or

 Patients intolerant to standard therapies due to severe side effects which negatively affect quality of life without providing an acceptable level of clinical benefit.

or

Patients in whom standard therapies are contraindicated.

OR

• Adult and pediatric post renal transplantation patients with nephrotic syndrome associated with primary FSGS.

# 1.5 Warnings

- 1. Before using the LIPOSORBER® LA-15 System, carefully review the instructions for use provided for each of the disposables and this Operator's Manual. Persons performing the procedures must be qualified to perform extracorporeal procedures, and have completed the required training program. Users should follow all operating or maintenance procedures published by Kaneka Pharma America LLC and use only the disposable device components recommended by Kaneka Pharma America LLC. Failure to do so may result in injury or loss of life.
- 2. LDL-apheresis treatment of patients who have taken any antihypertensive drugs within 24 hours of treatment may cause hypotension in such patients. When clinically feasible, patients should not receive antihypertensive drugs during the 24-hour period prior to undergoing the LDL-apheresis procedure. Before each treatment, physicians should determine when patients took their last dose of such medication.
- 3. The storage and use of this disposable device other than in accordance with the instructions published by Kaneka Pharma America LLC or the use of disposable device components not recommended by Kaneka Pharma America LLC may result in serious patient injury or loss of life. The manufacturer and distributor(s) of the disposable devices will not be responsible for patient safety if the procedures to operate and maintain the LIPOSORBER® LA-15 System are other than those specified in the instructions for use and this Operator's Manual.
- 4. During an LDL-apheresis procedure, 0.9% Sodium Chloride Injection, USP, 5% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP, and Heparin Sodium Chloride Injection, USP, are used. Carefully identify each solution and ensure that it is properly connected to the LIPOSORBER® LA-15 System. Using the incorrect solution may result in serious injury or possible death.
- 5. The disposables are **intended for use in a single procedure only. Never reuse.**Discard the disposables after each use.
- 6. The LIPOSORBER® LA-15 System may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended to at all times by a physician or qualified health-care professional adequately trained in all aspects of the procedure.
- 7. Rinsing and subsequent priming of the fluid pathway of the disposables with appropriate solutions are necessary before commencing the procedure. Because air bubbles in the disposables may lead to complications such as coagulation of plasma and impairment of performance, give full attention to measures that will prevent air bubble migration into the disposables during rinsing and priming.
- 8. While operating, the differential pressure across the LIPOSORBER® LA-15 LDL Adsorption Column must be under 100 mmHg, and the transmembrane pressure (TMP) of the SULFLUX® KP-05 Plasma Separator must be under 60 mmHg. If either an extreme rising of the differential pressure across the column or extreme rising of the TMP occurs, the blood flow rate and/or plasma separation rate should be lowered appropriately or even stopped if necessary.

- 9. Citrate preparation (ACD) should never be used as an anticoagulant in the system. The LIPOSORBER® LA-15 System is designed solely for treatment using heparin as an anticoagulant. Anticoagulation is required to prevent thrombus formation from occurring within the extracorporeal circuit. Anticoagulation with too much heparin is associated with an increased risk of bleeding for the patient, especially after the procedure. In order to reduce the risk of bleeding, the puncture sites should be sufficiently compressed so that bleeding is stopped. (See Section 1.7 Adverse Events) In some patients the potential for development of a coagulopathy extending several days post-therapy may exist. In addition to adjusting heparin dosage based on clinical observation during and after the apheresis procedure, Activated Clotting Time and/or partial thromboplastin time (PTT) values may be used. (See Section 1.9.2 Instructions for Use regarding "Determining Heparin Dosage")
- 10. To minimize the risk of air embolism, the return tubing line must be connected to the air bubble detector.
- 11. No chemicals or solvents are to be used either inside or outside of the disposables.
- 12. Due to the risk of reduction of blood pressure with the LIPOSORBER® LA-15 System, extra caution should be exercised in use of the device in patients with systolic and/or diastolic blood pressure ≤ 5<sup>th</sup> percentile for age, gender and height.
- 13. Use special caution in patients where the extracorporeal volume of approximately 400 ml potentially will exceed 10% of the patient's blood volume. Such patients are at higher risk of experiencing hypovolemia, which is sometimes followed by hypotension.
- 14. In case of a power failure or system shutdown, terminate the procedure immediately according to the instructions provided in Section <u>7.6 Manual Blood Return</u> of this Operator's Manual.
- 15. The safety of LDL-apheresis treatment with the LIPOSORBER® LA-15 System occurring more than twice a week or for treated volumes larger than 60mL/kg patient plasma volumes in FSGS has not been established.
- 16. Do not apply whole blood directly to the LIPOSORBER® LA-15 LDL Adsorption Column. The column is designed for perfusion of plasma only.
- 17. Make sure that the plasma flows in the direction of the arrow on the label of the LIPOSORBER® LA-15 LDL Adsorption Column.

## 1.6 Precautions

- 1. The need for the administration of angiotensin receptor blockers (ARBs) prior to the treatment on the day of the apheresis treatment should be determined by the treating physician. If the treating physician determines that it is not necessary, the patient should not take ARBs on the day of the apheresis treatment until the apheresis treatment is completed in order to minimize the risk of a hypotensive reaction during the extracorporeal therapy.
- Medical personnel should monitor the patient for adverse symptoms at all times during treatment and should be trained as to the protocol for responding with appropriate interventions. (See Section 1.7 Adverse Events)
- 3. All connections of the extracorporeal circuit should be checked carefully prior to initiating and during the procedure. Avoid unnecessary kinking of the tubing lines and the patient's vascular access devices at all times.
- 4. The transducer protectors must be attached and locked to the machine and tubing lines. Strict aseptic technique should be used during this and all procedures. After the completion of the procedure, properly dispose of all used and unused transducer protectors. Do not reuse.
- 5. Each tubing line must be properly connected and cleared of air, prior to the start of Rinse. Do not allow air to be trapped in the set. Puncturing tubing lines may cause air embolism.
- 6. Drip chambers in the extracorporeal circuit should be kept at least 2/3 to 3/4 full and monitored at all times in order to decrease the risk of air embolism.
- 7. The fluid circuit of this system is intended to be sterile and nonpyrogenic. Aseptic handling techniques are necessary to maintain these conditions. Prior to use, carefully examine the packaging of the disposable device components to ensure that it is intact and undamaged. Do not use a disposable product if the package, sterile bag, protective cap or the product itself is not intact or is damaged. Do not open the sterile bags containing the disposables until immediately prior to use.
- 8. The safety and probable benefit of LDL-apheresis using the LIPOSORBER® LA-15 System in FSGS have not been established for: (1) patients less than 21 kg in body weight; (2) patients less than 5 years of age; (3) patients with certain cardiac impairments such as uncontrolled arrhythmia, unstable angina, decompensated congestive heart failure or valvular disease; and (4) patients with thyroid disease or liver abnormalities.
- The safety and probable benefit of LDL-apheresis using the LIPOSORBER® LA-15
   System in FSGS have not been established for pregnant women or for women during the
   lactation period, e.g. the effect of treatments on folic acid levels has not been
   determined.
- 10. Closely monitor patient clotting time periodically during the procedure to ensure that an adequate level of anticoagulation is maintained.
- 11. Instructions for heparin administration should be followed as stated in the guidance provided by the manufacturer in this Operator's Manual. The amounts of heparin outlined in this Operator's Manual are intended as general suggestions. The exact amount, frequency and method of administration of heparin are the sole responsibility of the prescribing/attending physician and should be selected based on the individual patient's clinical condition.

- 12. Physicians and operators should follow the OSHA and the CDC/ACIP Adult Immunization Guidelines for Hemodialysis Patients. It is recommended that patients be screened for Hepatitis B and other infectious diseases; however, due to possible exposure to hepatitis virus, human immunodeficiency virus, and other infectious agents when handling extracorporeal blood circuits, blood or blood products, universal precautions should be taken at all times to prevent the exposure to and transmission of such agents.
- 13. When disposing of the disposable device components and wastes, comply with all local requirements and the policies of the facility regarding precautions for and prevention of infection and environmental pollution.
- 14. In transporting and storing the disposables, handle with care. Store all disposables in a clean and secure area at room temperature, avoiding exposure to direct sunlight, high humidity or excessive vibration. Handle the disposables with care to avoid dropping or other sudden impacts and never allow them to freeze. Do not use disposables which may have been dropped, damaged or frozen.
- 15. The disposables must never be used after the expiration date.
- 16. The LIPOSORBER® LA-15 System includes a blood warmer with a temperature setting range of 35-40 °C. It is recommended that the blood warmer be set at a temperature between 36-38 °C in order to avoid significant decreases in blood temperature during extracorporeal circulation.
- 17. Anemia may be minimized by the appropriate use of iron supplements.

## 1.7 Adverse Events

Adverse events that may be associated with the use of the LIPOSORBER® LA-15 System in FSGS include, but are not limited to, those listed in the following paragraphs. If a patient experiences an adverse reaction during a procedure, the physician should stop the procedure until the cause of the reaction has been determined and the patient's condition stabilized. The physician should determine all medical responses to adverse reactions based upon the individual patient's physical condition.

- 1) Death
- 2) Cardiac: Various abnormal heart rhythms may develop including bradycardia, tachycardia, and other arrhythmias. Myocardial infarction is another potential adverse cardiac event. If these are detected by vital sign monitoring, physical examination, or electrocardiography, immediate assessment and continued monitoring is essential.
- 3) Thrombocytopenia
- 4) Catheter-related adverse events: Use of the device requires a central venous access (catheter) for children and for some adults given their small venous caliber. Infection of the catheter may occur due to exit site infection, catheter-related bloodstream infection (CRBSI), improper use of the catheter, or internal catheter infection. Aseptic technique is required for catheter use. If an infection or bacteremia is suspected, culture of the catheter ports, in conjunction with peripheral culture (optional), is required. Antibiotic therapy should be provided according to physician discretion. Also, there are other adverse events associated with catheter use (e.g., hemothorax, pneumothorax, blood loss, arterial puncture, superior vena cava syndrome, arrhythmia, central venous stenosis, thrombosis and loss of potential fistula access).
- 5) Hypersensitivity (anaphylactoid) reaction: Use of angiotensin-converting enzyme inhibitors (ACEi) within 24 hours of therapy with the device can cause an increase in bradykinin levels, resulting in severe hypotension. ACE inhibitors should not be taken within 24 hours of therapy with the device.
- 6) Nausea and Vomiting. The procedure should be stopped and the etiology of the nausea and vomiting investigated (e.g., hypotension).
- 7) Reduction in Vitamin E level
- 8) Transient decrease in serum protein and albumin level
- 9) Hypotension: The procedure should be stopped, and the patient should be placed in the Trendelenburg position and/or receive a fluid challenge. If the hypotension persists, the procedure should be terminated. Note: For an "anaphylactoid" reaction, administration of epinephrine, sympathomimetic drugs, prednisolone, anti-histamines, and/or calcium have been reported by clinicians as effective interventions.
- 10) Abdominal symptoms. Patients may exhibit nausea, vomiting abdominal discomfort. These events should be addressed with conservative management and supportive care. The procedure should be stopped and the etiology of the nausea and vomiting investigated (e.g., hypotension).
- 11) Flushing/blotching: Check vital signs and reduce the blood flow rate. If symptoms are persistent or repetitive, consider the administration of diphenhydramine (e.g., Benadryl).

- 12) Angina/chest pain: The procedure should be stopped and medical therapy instituted at the discretion of the physician. If the angina persists, the procedure should be terminated.
- 13) Fainting/lightheadedness: See hypotension.
- 14) Anemia: May be minimized by the appropriate use of iron supplements.
- 15) Prolonged bleeding (at cannulation site after removing venous cannulae): Direct manual pressure should be applied until the bleeding stops. If prolonged bleeding occurs (in excess of 20 minutes), adjustment of the heparin dosing may be necessary. It is recommended that, during the subsequent procedure, the heparin dose be reduced and monitored by Activated Clotting Time (ACT). Repetitive LDL apheresis treatment may affect the patient's clotting time. Therefore, a periodic check, of other relevant coagulation parameters is recommended, including the number of thrombocytes and the fibrinogen concentration, in order to ensure that these parameters are sufficient to maintain adequate coagulation.
- 16) Hemolysis: as evidenced by discoloration of plasma or hemolysis as Indicated by activation of the blood leak detector alarm of the MA-03. If either indicator of hemolysis occurs, the procedure should be terminated and the patient's hematocrit, urine output and kidney function monitored.
- 17) Device malfunction: The system contains various components, including LDL apheresis columns (2), plasma separator, tubing system, and an electronic control unit. System malfunction may occur due to any of these components. If system malfunction occurs, the patient's vital signs and clinical status should be monitored immediately and repeatedly. It may be necessary to suspend treatment if the patient develops symptoms or if the problem cannot be readily solved.
- 18) Vertigo
- 19) Diaphoresis
- 20) Urticaria: Mild discomfort may occur requiring supportive care. Vital signs and physical examination of the patient are required in order to assess if urticaria is a component of a more severe, generalized reaction to the therapy. Specific associated symptoms, including, but not limited to, difficulty breathing, chest pain, and dizziness should be addressed by the physician.
- 21) Shivering
- 22) Headaches

# 1.8 Clinical Data

Clinical data to support the safety and probable benefit of LIPOSORBER® LA-15 System for FSGS can be divided to pre-transplant FSGS and post-transplant FSGS.

#### **1.8.1 Adults**

Published Clinical Studies of LIPOSORBER® LA-15 System Treatment for Patients with Nephrotic Syndrome (NS) and FSGS in adults are summarized in the table below.

Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre- transplant or Post- transplant
Muso 2015 [1] Muso 2015 [2]	44 (26 with FSGS)	Prospective Multicenter Single arm	Immediate to 2 years after treatment	Urinary Protein (UP) decreased from 6.28 ± 2.96 to 3.46 ± 3.34 g/day. 21/44 patients (48%) had a favorable 2-years outcome.	Pre- transplant
Muso 2001 [3] Muso 1999 [4]	17 (14 with FSGS)	Prospective Multicenter Controlled	Immediate to 2 years after treatment	UP decreased from 6.2 ± 3.3 to 2.7 ± 2.7 g/day.  The rate of achieving complete or incomplete remission was 71%.  As for the 2-years outcomes, 13/17 patients (76%) maintained UP <1.0 g/day.	Pre- transplant
Yokoyama 2002 [5]	6 (2 with FSGS; 1 treated with LIPOSO RBER®)	Prospective Single Center	Unknown	This was a prospective study of the effects of lymphocytapheresis in treating various forms of NS in 6 patients. One patient with FSGS failed to respond to one month of LIPOSORBER® treatment.	Pre- transplant
Nakamura 2006 [6]	8 FSGS	Prospective Single Center	2 weeks	UP decreased from 8.8 ± 4.2 g/day to 2.0 ± 1.2 g/day.	Pre- transplant

Study  Muso 2007 [7]	No. of Patients 41 FSGS	Study Design Retrospective	Length of Follow-up  5 years	At 1 month after LDL apheresis UP was significantly decreased.  Remission of nephrotic syndrome was observed	Pre- transplant or Post- transplant Pre- transplant and Post- transplant
				in 18/29 patients (62%) followed at 2 years and 13/15 patients (86%) followed at 5 years.	
Case Studie			<u> </u>	T	
Masutani 2005 [8]	1 FSGS	Case Report	1 year	LIPOSORBER® in conjunction with drug treatment resulted in reduction of UP from 6.8 g/day to 2.0 g/day.	Post-trans plant
				Incomplete remission had been maintained for more than 1 year.	
Miura 2009 [9]	1 FSGS	Case Report	40 days	Six cycles of hemodialysis were performed in conjunction with 4 cycles of LIPOSORBER® treatment. UP and serum creatinine levels recovered to normal values, and UP became undetectable by 40 days post-treatment.	Pre-transp lant
Miyazono 2008 [10]	1 FSGS	Case Report	Unknown	After 6 treatment sessions, the patient's UP decreased to non-nephrotic level. Furthermore, the patient's hypoproteinemia improved and renal function returned to normal. Although the patient experienced a relapse of nephrotic syndrome, 6 more sessions of LIPOSORBER® treatment brought the UP down to 0.8 g/day.	Pre-transp lant

Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre- transplant or Post- transplant
Tsukada 2006 [11]	1 FSGS	Case Report	Unknown	The patient underwent 8 sessions of treatment using LIPOSORBER®, which resulted in the reduction of the UP level and improvement of renal functions.	Post-trans plant
Haikal 2016 [12]	1 FSGS	Case Report	5 months	Partial remission sustained 5 months post therapy	Pre-transp lant

#### 1) Pre-transplant FSGS

(i) Muso et al. (2001) [3]: This study describes the comparison of efficacy between the treatment with the LIPOSORBER® LA-15 System in combination with steroids (LDL-A group) and that with steroids only (steroid monotherapy (SM) group) for patients with nephrotic syndrome who did not respond to full-dose (prednisolone, daily 1 mg/kg b.w.) therapy of 1-month duration under the fixed treatment protocol. The LDL group consisted of 17 patients (FSGS: 14, minimal change nephrotic syndrome (MCNS): 3) who were treated with the LIPOSORBER® LA-15 System. Treatments were performed twice a week for 3 weeks followed by weekly treatment for 6 weeks. The SM group included 10 patients (FSGS: 9, MCNS: 1) who were treated only with continuous full-dose steroids.

#### Results

#### Effectiveness:

- Total cholesterol (TC) level in the LDL-A group was significantly decreased after the treatment (337  $\pm$  118 to 242 $\pm$ 45.2 mg/dL, p=0.006), whereas decrease of TC level in the SM group was not significant (448 $\pm$ 106 to 366 $\pm$ 159 mg/dL, p=0.169).
- Hypoalbuminemia significantly improved in the LDL-A group (2.7±0.7 to 3.1±0.7 g/dL, p=0.014), while almost no change was noted in the SM group (2.8±0.4 to 2.9±0.7 g/dL, p=0.822).
- Proteinuria was significantly ameliorated in the LDL-A group (6.2±3.3 to 2.7±2.7 g/day, p=0.0008), while significant amelioration of proteinuria was not observed in the SM group (8.7±4.0 to 8.2±7.7 g/day, p=0.85).
- Average duration needed for a decrease of urinary protein to <3.5 g/day was significantly shorter in the LDL group than in the SM group (14.7±19.6 days vs 47.8±6.9 days, p=0.002).
- At the end of the treatment period, 9 patients (52%) in the LDL-A group achieved urinary protein level <1.0 g/day, whereas only 1 patient (10%) showed the same level in the SM group.
- As for the long-term outcomes (2 years after the end of the treatment period), 13 out of 17 patients (76%) maintained urinary protein level <1.0 g/day in the LDL-A group, compared to only 2 in 9 patients (22%) in the SM group.

#### Safety:

• The incidence of adverse events was not reported.

#### Conclusion

Superiority of therapeutic efficacy of the treatment with the LIPOSORBER® LA-15 System in combination with steroids to that with steroids alone was demonstrated in controlled study.

This study was a follow-up of the multicenter study reported by Muso et al (Kidney Int) in 1999. In this study, the authors did not report any adverse events.

Summary: Among the 17 patients with FSGS, short-term and medium-term efficacy data were provided compared to controls. Adverse events were not mentioned in the report.

(ii) Nakamura et al. (2006) [6]: This study investigated the effect of LIPOSORBER® LA-15 System in treating FSGS as part of a larger study to determine whether the levels of urinary liver-type fatty acid-binding protein (L-FABP) are associated with the severity of nephrotic syndrome. At the beginning of the study, all FSGS patients received 60 mg/day prednisone for 6 months, followed by either cyclophosphamide or mizoribine for another 6 months. Treatment with LIPOSORBER® LA-15 System was performed in 8 patients with drug-resistant FSGS twice a week for 3 weeks, then once a week for 6 weeks. In each 3-hour treatment session, 3000-4000 mL of plasma were treated. Renal function in terms of daily urinary protein excretion and serum creatinine levels were measured before the start of treatment and 2 weeks after the final treatment session.

#### Results

#### Effectiveness:

- Comparing the clinical parameters before and after the treatment, urinary protein and serum creatinine decreased significantly from 8.8  $\pm$  4.2 g/day to 2.0  $\pm$  1.2 g/day (p < 0.01) and from 123.8  $\pm$  26.5  $\mu$ mol/L to 97.2  $\pm$  17.7  $\mu$ mol/L (p < 0.05), respectively, and total protein increased from 40  $\pm$  8 g/L to 60  $\pm$  9 g/L (p < 0.01).
- In addition, serum level of L-FABP decreased from 122.6  $\pm$  78.4  $\mu$ g/gCr to 64.4  $\pm$  43.8  $\mu$ g/gCr (p < 0.05).

#### Safety:

 The article did not report any adverse events associated with LIPOSORBER® LA-15 System.

#### Conclusion

This study demonstrated that LDL apheresis therapy with LIPOSORBER® LA-15 System ameliorated proteinuria, hypoproteinemia, and renal function in drug-resistant FSGS.

This was a prospective study. Among the 8 patients with FSGS, encouraging short-term efficacy data were provided. A control arm was not included in this study. Adverse events were not mentioned in the report.

(iii) Muso et al. (2015) [1]: The investigators conducted a prospective, observational, multi-center cohort study (POLARIS study). In the POLARIS study, patients with nephrotic syndrome who did not respond to primary medication were registered before starting the treatment with LIPOSORBER® LA-15 System and clinical effectiveness and safety were examined. A total of 58 patients (who underwent 64 treatments) were registered in the study. Of the 64 treatment regimens, 17 were excluded for various reasons, leaving 47 treatment regimens for 44 patients available for analysis. As for FSGS, 23 patients were registered and underwent a total of 26 treatments. Clinical data were collected at baseline and after treatment with LDL-apheresis based on 24-hour urinalysis. Lipid profiles and clinical parameters were compared between before and after the treatment.

#### Results

#### Effectiveness:

- TC and LDL cholesterol (LDL-C) levels were significantly decreased after the treatment (331.10  $\pm$  113.25 to 210.38  $\pm$  77.4 mg/dL; p<0.01, 205.86  $\pm$  100.to 84 92.37  $\pm$  56.64 mg/dL; p<0.01, respectively), whereas the changes of triglyceride (TG) and HDL-cholesterol (HDL-C) were not significant (262.74  $\pm$  155.17 to 241.30  $\pm$  182.14 mg/dL; n.s., 69.49  $\pm$  22.58 to 73.64  $\pm$  23.40 mg/dL; n.s.).
- Hypoproteinemia (serum protein), hypoalbuminemia (serum albumin), and proteinuria (urinary protein) were significantly ameliorated immediately after treatment (4.42 ± 0.69 to 4.68 ± 0.81 g/dL; p<0.05, 2.15 ± 0.63 to 2.63 ± 0.79 g/dL; p<0.01, and 6.28 ± 2.96 to 3.46 ± 3.34 g/day; p<0.01, respectively). In addition, renal function (creatinine clearance) significantly improved immediately after treatment (58.59 ± 41.35 to 65.11 ± 41.39 mL/min; p<0.05).</li>
- Serum levels of fibrinogen and thrombin-antithrombin III complex (TAT) level were significantly reduced (374.46 ± 130.04 to 297.92 ± 108.87 mg/dL; p<0.01, 16.39 ± 33.60 to 12.21 ± 34.10 ng/mL; p<0.05, respectively) suggesting that treatment with LIPOSORBER® LA-15 System exerts anticoagulation activity.</li>

#### Safety:

• The incidence of adverse events was not reported.

#### Conclusion

LDL apheresis therapy with LIPOSORBER® LA-15 System rapidly ameliorated symptoms of nephrotic syndrome, i.e., proteinuria and hypoproteinemia, in more than half of the patients who failed to respond to primary medication.

This was a short-term study.

The endpoints were:

- Complete remission: Urinary Protein (UP) = undetectable
- Incomplete Remission I: UP < 1.0g/day</li>
- Incomplete Remission II: 1.0 g ≤ UP < 3.5 g/day</li>
- No effect: UP ≥ 3.5 g/day

In this study, complete or incomplete remission were considered favorable outcomes.

The average number of apheresis sessions was 9.6/patient. An average of 3.5 L of plasma was treated per session. Among the 44 patients, FSGS was the diagnosis in 23 (52.3%) of the patients.

(iv) <u>Muso et al. (2015) [2]:</u> The long-term (2 years) outcome of the POLARIS cohort was investigated for the 44 subjects. Of the 58 patients who were registered in the POLARIS study, 5 were excluded from the study because of protocol violation or inadequate data collection, 6 were lost to follow up, and 3 died during the follow-up period, thus leaving 44 subjects eligible for analysis at two years. As for primary diseases of the subjects, FSGS was found in the majority of cases, presenting in 28 subjects (63.6%).

#### Results

#### Effectiveness:

- Twenty-one (21) of the 44 subjects (47.7%) had a favorable outcome, with 11 subjects (25%) in complete remission (defined as urinary protein undetectable) and 10 subjects (22.7%) in incomplete remission I (defined as urinary protein level < 1.0 g/day). Twenty-three (23) subjects (52.3%) had an unfavorable result, with 11 (25%) in incomplete remission II (defined as 1.0 g/day < urinary protein < 3.5 g/day) and 12 (27.3%) with no effect (defined as urinary protein level > 3.5/day).
- An analysis was performed of the factors affecting outcome. The authors found that the urinary protein level post-treatment was strongly associated with 2-year outcome (p < 0.001). For subjects with favorable outcomes, the urinary level after treatment was  $1.68 \pm 1.76$  g/day compared to  $6.18 \pm 3.24$  g/day for subjects with unfavorable outcomes.
- Improvement of parameters representing disease conditions of nephrotic syndrome, including serum albumin, eGFR, urinary protein and total and LDL cholesterol were all significantly associated with favorable outcome. This suggests that an early rapid alleviation of nephrotic syndrome by LDL-apheresis contributes to a favorable outcome.

#### Safety:

 No adverse event associated with LIPOSORBER® LA-15 System was reported in this report.

#### Conclusion

The POLARIS study demonstrated that LDL apheresis therapy with LIPOSORBER® LA-15 System ameliorates nephrotic conditions and that the therapeutic efficacy of LDL apheresis was largely maintained for two years.

During the time from the short- to long-term POLARIS study, 3 subjects died of diseases unrelated to NS (cerebral infarction, lung cancer and pneumonia). Given the variety of histological diagnoses in the patients included in the study, it was challenging to ascertain the outcomes for patients with FSGS versus those with other diseases. That said, the study does report that urine protein levels decreased significantly and similarly for patients with/without FSGS and this study provides reasonable assurance of efficacy of the device in about 50% of patients with FSGS.

#### 2) Post-transplant FSGS

Muso et al. (2007) [7]: This study describes 41 patients with refractory FSGS. The study population included a sub-set of 7 patients who developed recurrent FSGS after undergoing renal transplantation. The study was intended to evaluate the long-term outcome of LDL apheresis in patients with FSGS.

The study included the change in lab values (e.g., serum protein, serum albumin, proteinuria) at 1 month after treatment and measured the number of patients achieving remission of nephrotic syndrome at 2 and 5 years after LIPOSORBER® treatment. Although the investigators did not indicate that any of the patients included in the analysis were children, the results can be used to assess effectiveness in children as the course of the disease is sufficiently similar in both adults and children.

The criteria used to assess clinical response were:

- Remission of nephrotic syndrome (NS)
  - o Complete remission
  - Type I incomplete remission: proteinuria negative or < 1.0 g/day and serum albumin > 3.0 g/dL
  - Type II incomplete remission: proteinuria < 3.5 g/day but serum albumin</li>
     3.0 g/dL

#### Results

#### Effectiveness:

- At 1 month after LDL apheresis total serum protein and albumin increased significantly and proteinuria was significantly decreased.
- Remission of nephrotic syndrome was observed in 18/29 patients followed at 2 years (62%).
- Remission of nephrotic syndrome was observed in 13/15 patients followed at 5 years (86%).

The seven post-transplant patients were included in the 41 patients analyzed at 1 month. The authors did not analyze the data collected from pre- and post-transplant patients separately. Instead, the authors state that the exclusion of the post-transplant patient data did not impact the data trend or significance of the results, indicating that the post-transplant data were similar as a group to the pre-transplant patients in terms of increase in serum protein and albumin and decrease in proteinuria. The authors did not indicate the number of post-transplant patients included in the 2 and 5 years follow-up.

#### Safety

• The incidence of adverse events was not reported.

#### Conclusion

The authors conclude that early administration of LDL-apheresis after the onset of nephrotic syndrome associated with FSGS provides a good long-term outcome.

This was a retrospective study. Patients had drug-resistant (persistence of proteinuria  $\geq$  1.0 g/day after the initial treatment for at least 4 weeks) NS and FSGS. Of the 41 cases of NS due to FSGS, 20 were new-onset. The device treatment was provided in conjunction with standard medications for FSGS/NS: steroids, cyclosporine A, or other immunosuppressive medications. Each patient received 3-12 treatments with the device.

Adverse events (safety) were not assessed.

In summary, among the 41 patients, encouraging two-year efficacy data were provided for 29 patients (assuming constant enrollment) and five-year data were available for 15 patients. This may be due to steady enrollment throughout the study period.

## Safety Assessment

The studies above did not report reliable adverse event data. However, the safety data from adults with functional hypercholesterolemia (FH) treated with the device can be extrapolated to safety for adults with FSGS treated with the LIPOSORBER® LA-15 System. The table below demonstrates the rates of various adverse events in adults with FH treated with the LIPOSORBER® LA-15 System:

Adverse Event	Episodes		Pa	ntients
Hypotension	41	0.8%	25	33.8%
Nausea/Vomiting	27	0.5%	14	18.9%
Flushing/Blotching	20	0.4%	9	12.2%
Angina/Chest pains	10	0.2%	8	10.8%
Fainting	9	0.2%	6	8.1%
Lightheadedness	7	0.1%	6	8.1%
Anemia	6	0.1%	6	8.1%
Abdominal discomfort	5	0.1%	3	4.1%
Numbness/Tingling	4	0.1%	4	5.4%
Tachycardia	4	0.1%	3	4.1%
Headache	3	0.1%	3	4.1%
Shortness of Breath	3	0.1%	2	2.7%
Hemolysis	3	0.1%	2	2.7%
Bradycardia	3	0.1%	2	2.7%
Itching/Hives	2	0.04%	2	2.7%
Blurred Vision	2	0.04%	2	1.4%

#### 1.8.2 Pediatrics

Hattori et al. (2003) [13]: This study describes the outcomes of eleven (11) children with steroid resistant primary FSGS who were treated unsuccessfully with conventional-dose cyclosporine therapy and showed persistent nephrotic range proteinuria. At the time of treatment with the LIPOSORBER® LA-15 System, none of the patients had received a renal transplant ("pre-transplant"). At the start of the 7<sup>th</sup> apheresis treatment (average number of treatments: 11.5), prednisone was administered at a dose of 1mg/kg/d for 6 weeks, followed by a tapering schedule during subsequent months.

The effectiveness endpoint was the number of patients achieving remission of nephrotic syndrome. Other measures included renal function (i.e., GFR, degree of proteinuria, cholesterol level and complications of therapy.

The criteria used to assess clinical response were:

Remission of nephrotic syndrome (NS)

#### 1. INTRODUCTION

- Complete remission: reduction in urinary protein (< 4 mg/m²/h) for 3 consecutive days with normal serum albumin and cholesterol levels, and stable renal function
- Partial remission: lower urinary protein levels but persistent non-nephrotic proteinuria (protein< 40 mg/m²/h) with normal serum albumin</li>
- Renal Function (as GFR, in ml/min/1.73m<sup>2</sup>)
- Proteinuria (g/m²/day).

#### Results

#### Effectiveness:

- Achievement of remission (defined above) of nephrotic syndrome was observed in 7/11 patients (5 complete and 2 partial).
- Renal function (GFR) for the five (5) patients who achieved complete remission was normal during follow-up (median: 4.4 years, range: 4.0-11.1 years).
- Proteinuria declined in 7/11 patients (as evidenced by remission of nephrotic range proteinuria).

#### Safety:

• Only one patient developed a complication (infection of the indwelling catheter used to receive the therapy).

#### Conclusion

The authors suggest that combined LDL-apheresis and prednisone therapy can be a valuable therapeutic option for treating patients with steroid resistant FSGS.

#### References

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## 1.9 Instructions for Use

Use of the LIPOSORBER® LA-15 System in adult and pediatric patients with FSGS is recommended to occur twice weekly for 3 weeks followed by once per week for six weeks.

# 1.9.1 Determining Plasma Volume to be Treated

The clinical experiences in Japan suggest that treating 60 mL/kg patient plasma volumes during a single procedure is acceptable for adult and pediatric patients with primary focal segmental glomerulosclerosis. The plasma volume to be treated can be calculated as follows:

STEP 1: Obtain patient weight (kilograms)

STEP 2: Multiply the patient weight by 60.

STEP 3: Round up the value from Step 2 to the nearest hundredth.

This is the plasma volume to be treated.

## **Example:**

STEP 1: Obtain patient weight.

Weight: 48kg

STEP 2: Multiply value from STEP 1 by  $60 \rightarrow 48 \times 60 = 2,880$ 

STEP 3: Round up value from STEP 2 to the nearest hundredth  $\rightarrow$  2,900 ml

This is the plasma volume to be treated.

The amount of plasma treated will require adjustment as clinically indicated by the physician in order to achieve and optimize individualized patient treatment goals.

# 1.9.2 Determining Heparin Dosage

Although heparin administration procedures vary and are adjusted to the requirements of the individual patient by a supervising physician, a proper heparinization schedule **must be** initiated before and maintained throughout LDL-apheresis to prevent clotting and subsequent blood path obstruction. The following are examples of heparinization schedules.

- 1. <u>Priming Solution</u>. Lactated Ringer's Injection, USP (1,000 ml) should contain 2,000-3,000 USP units of heparin.
- 2. <u>Loading Dose (Manual Infusion)</u>. Obtain PTT and PT pretreatment levels prior to initiation of LDL-apheresis therapy. If values are in the normal range, the recommended loading dose is approximately 25 USP units of heparin per kilogram of body weight. If a patient's PTT or PT is abnormally high, the physician should consider a lower loading dose of heparin.
- 3. Continuous Heparinization. Continuous heparinization is required during the LDL-apheresis procedure. Based upon a normal PTT and PT, approximately 25 USP units of heparin per kilogram of body weight per hour is recommended. During the first few apheresis treatments, coagulation test results should be monitored frequently to establish a coagulation profile for the individual patient. A monitoring schedule for these initial treatments should consist of a pre-heparinization PTT, PT, and activated clotting time (ACT) measurement. The ACT measurements should be performed at 30-minute intervals during the treatment. ACT levels should be maintained within a range of 180-250 seconds or 1.5 to 3 times the normal range. Once a patient's heparin regimen has been established, a patient's ACT may be followed less frequently during subsequent treatments.

A heparin pump is used to deliver heparin into the blood withdrawal line at a rate necessary to maintain a desired clotting time. A heparin pump infusion rate between 1,000-3,000 USP units of heparin per hour usually is sufficient.

Detailed Instructions for Use are set forth in the accompanying Operator's Manual for the LIPOSORBER® LA-15 System and in the instructions for use for the LIPOSORBER® LA-15 LDL Adsorption Column, SULFLUX® KP-05 Plasma Separator, and Tubing System for Plasmapheresis (NK-M3R(U)). The procedures outlined in the Operator's Manual must be followed exactly as specified. No adjustments or modifications of such procedures not specifically stated in the Operator's Manual may be made. In the event of equipment or device failure or malfunction, discontinue the procedure and follow the instructions in the Operator's Manual.

# 1.10 Moving and Transportation of the MA-03

# **A**CAUTION

When moving the MA-03, do not put your feet close to the casters. They may get crushed.

# 1.10.1 Moving of the MA-03 Indoors

## Normal Moving

- Release the lock of casters.
- 2. After that, the MA-03 can be moved or turned freely.

# **A**CAUTION

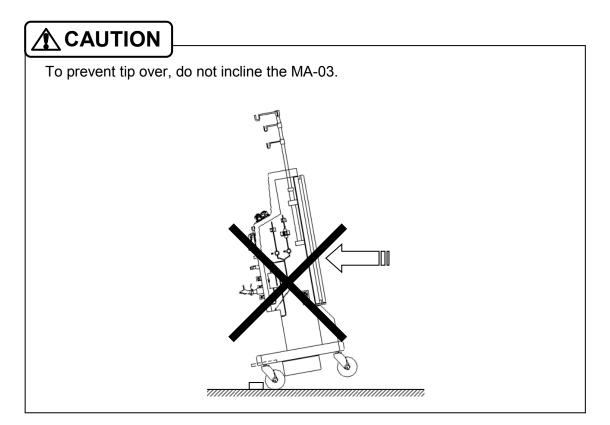
If moving the MA-03 down or up a slope (an angle over 10°), two people should be used.

# **⚠** CAUTION

When you move MA-03, please move the external lamp to the lowest position. And be careful not to hit the ceiling and the upper frame of the door.

## ■ Moving Over Different Floor Levels (i.e. Entrance of an elevator)

1. To prevent damage or falling of the machine, always move the machine slowly while rolling over different floor levels or small bumps.





Do not lift the machine by grasping the external lamp or bag hanger. This can damage the machine.

## 1.10.2 Transportation of the MA-03 Outdoors

- 1. The machine must not be moved across uneven surfaces (i.e., stone paved roads and the like).
- 2. If the machine needs to be moved across an uneven surface, protect it from vibration by placing the machine on a sturdy handcart with proper padding.
- 3. Before transporting the machine, remove all equipment and disposables such as solution bags, the external lamp and bag hangers.
- 4. "Power Failure" buzzer sounds if POWER ON Button was accidentally pressed while transporting the machine.



"Power Failure" buzzer stops when POWER OFF Button on the Operation Panel is pressed for more than 3 sec.

## 1.11 EMC information

The MA-03 conforms to the EMC standard of IEC60601-1-2:2001

## 1.11.1 Electromagnetic Emission and Electromagnetic Immunity

The MA-03 is intended for use in the electromagnetic environment specified below. The customer or the user of the MA-03 should assure that it is used in such an environment.

Emissions test	Compliance	Electromagnetic environment - guidance
RF emissions	Group 1	The MA-03 uses RF energy only for its internal
CISPR 11		function. Therefore, its RF emissions are very low and
		are not likely to cause any interference in nearby
		electronic equipment.
RF emissions	Class A	The MA-03 is suitable for use in all establishments
CISPR 11		other than domestic and those directly connected to the
Harmonic emissions	Class A	public low-voltage power supply network that supplies
IEC 61000-3-2		buildings used for domestic purposes.
Voltage fluctuations	Complies	
/ flicker emissions		
IEC 61000-3-3		

	Guidance – electromagnetic immunity				
Immunity test	IEC60601 test level	Compliance level	Electromagnetic environment - guidance		
Electrostatic discharge (ESD) IEC 61000-4-2	±6kV contact ±8kV Air	±8kV Air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30 %.		
Electrical fast transient / burst IEC 61000-4-4	±2kV for Power supply line ±1kV for input / output line	±2kV for Power supply line ±1kV for input / output line	Mains power quality should be that of a typical commercial or hospital environment.		
Surge IEC 61000-4-5	±1kV differential mode ±2kV common mode	±1kV differential mode ±2kV common mode	Mains power quality should be that of a typical commercial or hospital environment.		
Voltage dips, short interruptions and voltage variations on power supply input lines IEC 61000-4-11	<5% Ut (>95% dip in Ut) for 0.5 cycle  40% Ut (60% dip in Ut) for 5 cycle  70% Ut (30% dip in Ut) for 25 cycle  <5% Ut (>95% dip in Ut) for 5 s	5% <i>Ut</i> (>95% dip in <i>Ut</i> ) for 0.5 cycle  40% <i>Ut</i> (60% dip in <i>Ut</i> ) for 5 cycle  70% <i>Ut</i> (30% dip in <i>Ut</i> ) for 25 cycle  <5% <i>Ut</i> (>95% dip in <i>Ut</i> ) for 5 s	Mains power quality should be that of a typical commercial or hospital environment. If the user of the MA-03 requires continued operation during power mains interruptions, it is recommended that the MA-03 be powered from an uninterruptible power supply or a battery.		
Power frequency (50/60Hz) magnetic field IEC61000-4-8	3A/m	3A/m	Power frequency magnetic field should be measured in the intended installation location to assure that it is sufficiently low.		
NOTE Ut is the a.c. mains voltage prior to application of the test level.					

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	Guidance – electromagnetic immunity			
Immunity test	IEC60601	Compliance	Electromagnetic environment - guidance	
	test level	level		
			Potable and mobile RF communications	
			equipment should be used no closer to any part	
			of the MA-03 including cables, than the	
			recommended separation to the frequency of the	
			transmitter.	
Conducted RF	3Vrms	3Vrms	Recommended separation distance	
IEC61000-4-6	(150kHz		<i>d</i> =1.2√ <i>P</i>	
	to		<i>d</i> =1.2√ <i>P</i> (80MHz to 800MHz)	
	80MHz)		$d=2.3\sqrt{P}$ (800MHz to 2.5GHz)	
Radiated RF				
IEC61000-4-3	3V/m	3V/m	where <i>P</i> is the maximum output power rating of	
	(80MHz		the transmitter in watts (W) according to the	
	to		transmitter manufacture and <i>d</i> is the	
	2.5GHz)		recommended separation distance in meters (m) $(\sqrt{P})$ is a square root of P.)	
			Field strengths from fixed RF transmitters, as	
			determined by an electromagnetic site survey,"a"	
			should be less than the compliance level in each	
			frequency range."b"	
			Iterference may occur in the vicinity equipment	
			maked with the following symbol:	
			$\left(\left(\left(ullet\right)\right)\right)$	

NOTE 1 At 80MHz and 800MHz, the higher frequency range applies.

NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.

"a" Field strengths from fixed transmitters, such as base stations for radio (cellular / cordless) telephones and land mobile ratios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered If the measured filed strength in the location in which the MA-03 is used exceeds the applicable RF compliance level above, the MA-03 should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as re-orienting or relocating the MA-03.

"b" Over the frequency range 150kHz to 80MHz, it is preferable that the field strengths should be less than 3 V/m.

# 1.11.2 Recommended separation distances between portable and mobile RF communications equipment and the MA-03

The MA-03 is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or the user of the MA-03 can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the MA-03 as recommended below, according to the maximum output power of the communications equipment.

Rated	Separation distance according to frequency of transmitter			
maximum	m			
output power	150kHz to 80MHz	80MHz to 800MHz	800MHz to 2.5GHz	
of transmitter	<i>d</i> =1.2√ <i>P</i>	<i>d</i> =1.2√ <i>P</i>	<i>d</i> =2.3√ <i>P</i>	
W				
0.01	0.12	0.12	0.23	
0.1	0.38	0.38	0.73	
1	1.2	1.2	2.3	
10	3.8	3.8	7.3	
100	12	12	23	

For transmitters rated at a maximum output power listed above, the recommended separation distance *d* in meters (m) can be estimated using the equation applicable to the frequency of the transmitter, where *P* is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.

NOTE 1 At 80MHz and 800MHz, the separation distance for higher frequency range applies.

NOTE 2 These guidelines may no apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.

## 1.12 The MA-03 Danger, Warning and Caution

# **⚠** DANGER

Do not use the machine where highly flammable anesthetic or flammable gas is used, in a high pressure oxygen room or in oxygen tent.

This could trigger an explosion.

# **MARNING**

Use of Machine by an unqualified operator may result in injury or death to the patient and the operator, or damage to the MA-03.

# **MARNING**

Grounding reliability can only be achieved when the machine is connected to an equivalent receptacle marked "Hospital only" or "Hospital grade".

Never use any adaptor which breaks the contact between the machine ground and the receptacle ground.

When not grounded, this could cause electric shock.

# **WARNING**

In the machine's vicinity, never use devices that cause electromagnetic interference, such as mobile phones, CB wireless transmitters, electric cauteries or defibrillators while the machine is in operation. The machine may malfunction.

# **⚠** WARNING

If any device which transmits electromagnetic wave is used around the MA-03, this may cause the MA-03 to malfunction.

Please follow instructions indicated in section 1.11 of this manual.

## **MARNING**

Use only authorized accessories for the machine.

If an improper accessory is connected to the MA-03, physical injury may result.

# **MARNING**

The machine can not be used if a defibrillator needs to be used on the patient.

Do not touch the machine when discharging the defibrillator.

Confirm proper operation of the machine after defibrillator use. Use of a defibrillator could negatively affect the machine's safe operation.

# **MARNING**

Only use specified power supply voltage otherwise fire or electric shock may occur.

# **MARNING**

Do not open access covers of the MA-03.

This could cause fire or electric shock.

# **MARNING**

Do not place heavy apparatus on the power cord.

This could cause fire or electric shock.

# **MARNING**

A new, sterile transducer protective filters should be attached to all pressure ports.

This will prevent cross infection to patients through the machine.

If the transducer protective filters are wet and air is not able to pass, replace the transducer protective filter with a new one and clear the monitor line.

## **WARNING**

If the external transducer protective filter, internal transducer protective filter and the internal transducer are contaminated with blood replace the filter with a new one and sterilize or replace the transducer and the associated parts.

Only authorized KANEKA PHARMA AMERICA LLC service personnel should perform any parts replacement or sterilization.

# **↑** WARNING

Pressure changes resulting from line separation or needle removal may be too subtle for the system to detect.

All connections must be properly secured and visually confirmed regularly.

Access sites and connections should remain uncovered for monitoring.

# **⚠** WARNING

Instructions for operation:

- 1. The operator must confirm and verify that the indicated value is equal to the entered value every time the operator sets a parameter.
- 2. If the indicated value is not equal to the entered value, treatment must not be started in any case.

# **MARNING**

Make sure fluid is not poured or splashed on the machine.

# **⚠** WARNING

Maintenance:

Only authorized KANEKA PHARMA AMERICA LLC service personnel should perform assembly, installation, adjustment, or repair of the machine.

# **A** CAUTION

The machine should be installed in the following locations:

- 1. Level and stable location.
- 2. A location with three (3) feet of space around the machine to let air circulate.
- 3. Ambient temperature should be between 50-95 degrees Fahrenheit and the humidity should be less than 85%.
- 4. A location for properly grounding the machine.

# **A**CAUTION

The machine should not be installed in the following locations:

- A location where the machine is exposed directory to the sunlight for a long time. Especially, the LCD in the machine will be deteriorated by the ultraviolet ray of the sunlight. Therefore, do not leave the machine under direct sunlight for a long time.
- 2. A location where the machine is affected by splashed water or steam.
- 3. A location affected by vibrations and shocks.
- 4. A location where there is flammable or corrosive gases and fire.
- 5. A location where chemicals are stored.

## **A** CAUTION

If there is dew condensation on the machine, dry it well before turning the electric power on. Electric shocks could occur.

# **A**CAUTION

While in use, constantly monitor the machine for safe and proper usage.

## **⚠** CAUTION

Do not use ballpoint pens or other sharp-pointed objects to push the switches (buttons and keys). This may damage the front panel.

# **⚠** CAUTION

Be sure to handle electric plugs properly, or electric shocks and fire may occur:

- 1. Never handle electric plugs with wet hands.
- 2. When pulling electric plugs, do not pull the cord.
- 3. If the machine will not be used for a long time, unplug the power cord.

## **⚠** CAUTION

When cleaning the machine, do not use solvents like thinner and benzene and the like. The machine's surface may become damaged.

# **A** CAUTION

Set the bag hangers lower than six (6) feet of height to minimize the risk of the machine tilting over.



Measure for LCD's abnormality

If the LCD screen does not display any contents or a key has no response, turn off the machine immediately and then perform blood return by using the manual pump handle. (Please refer to Chapter 7.6 Manual Blood Return of the operator's manual )

[Operating keys in abnormal state of the LCD screen may lead to an unintended action of the machine.]



Do not leave the machine near the ultraviolet-rays sterilization light for a long time. [Ultraviolet-rays causes a deterioration or discoloration of the plastic parts on the outer surface and the LCD, and that causes a malfunction of the machine.]

### **Side Panel Caution Label**

A caution label is located at the position shown in Figure 1.1. Before operating the MA-03, read the label.

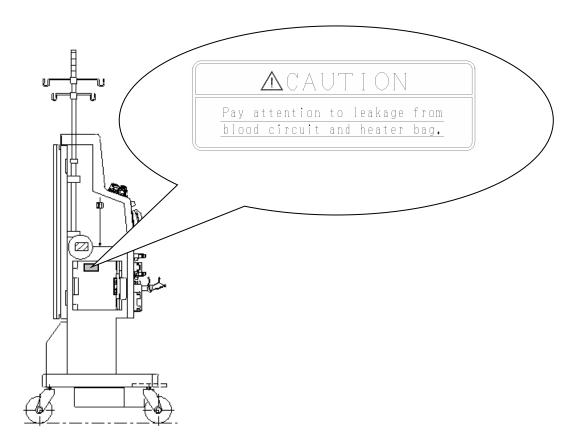


Figure 1.1 Caution Label

## 1.13 Limits to the Manufacturer's Responsibility

- The LIPOSORBER® LA-15 System must be used in accordance with this Operator's Manual. The use of operating or maintenance procedures other than those published by Kaneka Pharma America LLC or the use of disposable device components not recommended by Kaneka Pharma America LLC may result in injury or loss of life. Kaneka Pharma America LLC, the manufacturers of the MA-03 or the disposable device components, or any distributor of the LIPOSORBER® LA-15 System will not be responsible for resulting injury or damage if the procedures to operate and maintain the LIPOSORBER® LA-15 System are other than those specified in the instructions for use provided for each of the disposables and this Operator's Manual. Persons performing the procedures must be appropriately trained and qualified.
- In no event shall Kaneka Pharma America LLC or the manufacturers of the MA-03 or of the disposable device components or any distributor of the LIPOSORBER® LA-15 System be liable for any losses or damages caused or resulting from any negligence in the selection of patients outside the indicated population, operation of the LIPOSORBER® LA-15 System, or treatment of patients with the LIPOSORBER® LA-15 System by any third party.
- Except as expressly set forth herein, Kaneka Pharma America LLC makes no warranty whatsoever, express or implied, and specifically disclaims any warranty of merchantability or fitness for a particular purpose as to the LIPOSORBER® LA-15 System.
- Certain solutions and disposable products available from other manufacturers are used with the LIPOSORBER® LA-15 System. Kaneka Pharma America LLC has no control over variability, tolerances, mechanical strength or changes in these products which may exist from time to time. Therefore, Kaneka Pharma America LLC cannot ensure that the disposable products of other manufacturers will function in a satisfactory manner and expressly disclaims any responsibility or liability for any injury, harm, damages or loss resulting from the use or malfunction of such products.

### 1. INTRODUCTION

## 2. OVERVIEW OF THE MA-03

### 2.1 Environmental Conditions

### ■ Safe Operating Conditions

Ambient temperature 15 to 35°C

Relative humidity 30 to 85% (Non condensing)

Air pressure 700 to 1060hPa (0.66 to 1.0 atmospheres)

### ■ Safe Storage and Transportation Conditions

Ambient temperature -20 to 60°C

Relative humidity 10 to 95% (Non condensing)

# **A**CAUTION

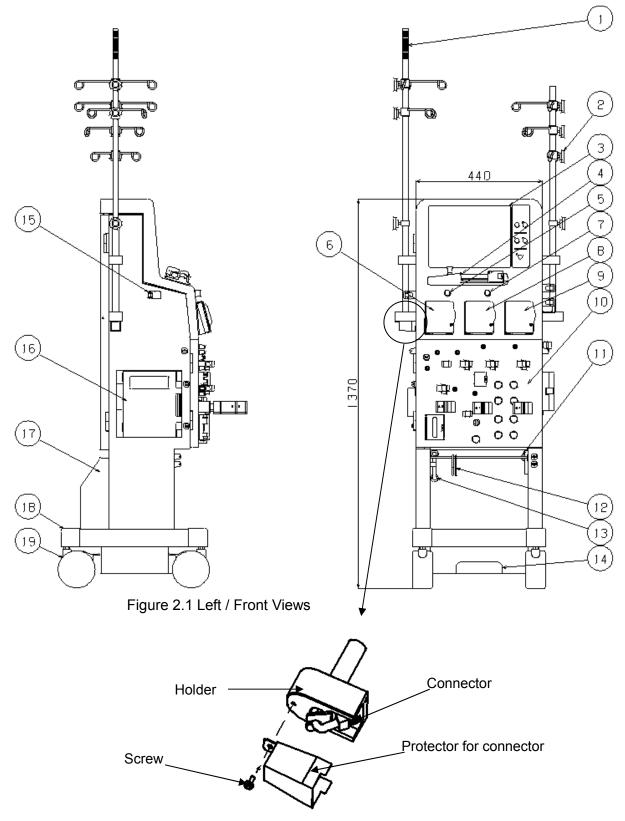
Particular attention should be given when storing the MA-03 for more than 15 weeks or when transporting.

### ■ Electric Power Supply (Electric Facility)

Nominal voltage	Frequency	Current	
115V AC	50/60Hz	5A	

## 2.2 Configurations of the MA-03

## 2.2.1 Appearance

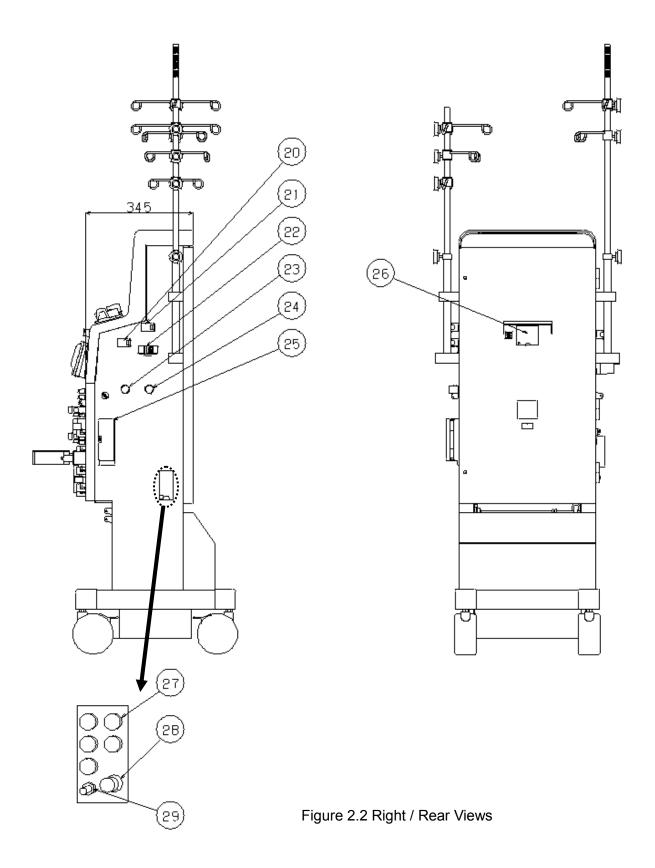


- 1. External Lamp
- 2. Bag Hanger
- 3. Monitor/Operation Panel (see "Monitor/Operation Panel" in Section 2.3.2.)
- 4. Infusion Pump (IP) (see "Infusion Pump" in Section 2.3.5.)
- 5. Blood Flow Rate Turning Knob
- 6. Blood Pump (BP) (see "Blood Pump, Plasma Pump and Replacement Fluid Pump" in Section 2.3.4.)
- 7. Plasma/Replacement Fluid Flow Rate Turning Knob
- 8. Plasma Pump (PP) (see "Blood Pump, Plasma Pump and Replacement Fluid Pump" in Section 2.3.4.)
- 9. Replacement Fluid Pump (RP) (see "Blood Pump, Plasma Pump and Replacement Fluid Pump" in Section 2.3.4.)
- 10. Front Panel (see "Front Panel" in Section 2.3.3.)
- 11. Power Cord
- 12. Hook for Waste Bag
- 13. Manual Pump Handle
- 14. Waste Fluid Container Table
- 15. Fluid Detector 1 (FD1)
- 16. Blood Warmer (Plate Heater; PH)
- 17. Box for the Operator's Manual
- 18. Rubber cap
- 19. Caster



Procedure to detach the external lamp (with bag hanger):

- Remove connector protector and disconnect connector. Protector is held by a screw.
- Loosen pole screw and lift pole upward.



- 20. Fluid Detector 2 (FD2)
- 21. Fluid Detector 3 (FD3)
- 22. Drip Detector (DD)
- 23. Replacement Fluid Valve (V1)
- 24. Regeneration Fluid Valve (V2)
- 25. Conductivity Detector (CD)
- 26. Data logging unit
- 27. Fuses
- 28. System-Start Switch
- 29. Connection Terminal for Potential Equalization Conductor



### System-Start Switch:

If the built-in battery is completely discharged and the MA-03 will not power on after pressing the POWER ON button, press this switch.

### Connection Terminal for Potential Equalization Conductor:

The connection terminal for potential equalization conductor is the terminal which connects to the potential equalization bus-bar from the electrical installation.

### 2.2.2 Monitor/Operation Panel

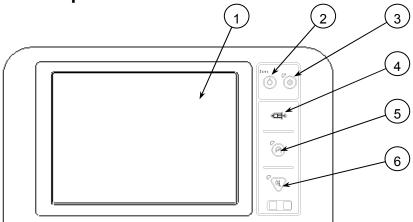


Figure 2.3 Monitor/Operation Panel

#### 1. LCD

Contents displayed on the LCD vary depending on the selected process, and the status of the alarm function. By touching keys on the LCD the MA-03 can be operated and conditions are set.



Operation of the MA-03 and setting of certain operating conditions can be managed on the LCD where information, instructions and alarm status are shown with text or graphics.

#### 2. POWER OFF Button

When this button is continually pressed for 3 seconds or longer, the MA-03 powers OFF.

#### 3. POWER ON Button with Operating Lamp

Press this button to power ON the MA-03. The operating lamp lights while the MA-03 is ON.

#### 4. INFUSION PUMP Indicator

The indicator lights or flashes while the Infusion Pump is operating.

#### 5. BLOOD PUMP Button and Indicator

This button is only active and the indicator lamp is lit in the processes of Rinsing, Priming, Treatment and Return. When this button is pressed while active, the machine enters into "Process Suspended" status, and all pumps stop and all valves close. The indicator lamp blinks and the "Process is suspended" screen appears on the LCD. To resume the process, press this button again.

#### 6. MUTE Button and Indicator

While the alarm buzzer is sounding, press this button to mute the buzzer for up to 2 minutes. If another alarm-triggering event occurs during that period, the alarm buzzer sounds again. The indicator flashes while the alarm buzzer is muted.

# **A** CAUTION

While an "Alarm" condition exists, the "Process is suspended" screen is replaced with the "Alarm" screen. The "Process is suspended" screen will appear when all alarm conditions are resolved.

## 2.2.3 Front Panel

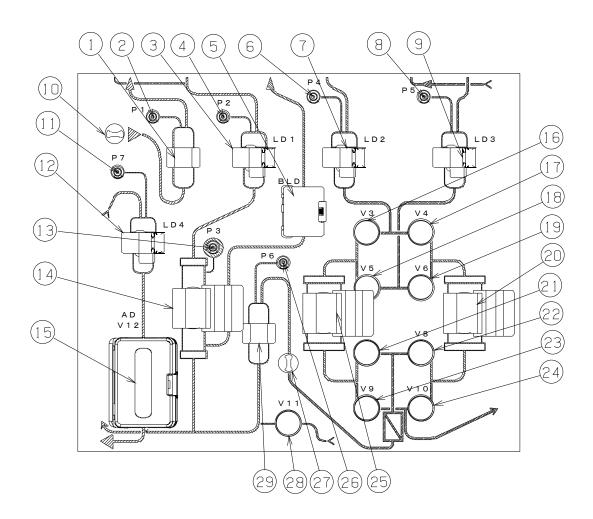
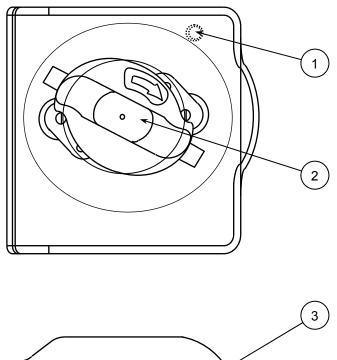


Figure 2.4 Front Panel

- 1. Arterial Chamber Holder
- 2. Arterial Pressure Port (P1)
- 3. Blood Inlet Level Detector (LD1)
- 4. Blood Inlet Pressure Port (P2)
- 5. Blood Leak Detector (BLD)
- 6. Plasma Inlet Pressure Port (P4)
- 7. Plasma Inlet Level Detector (LD2)
- 8. Replacement Fluid Pressure Port (P5)
- 9. Replacement Fluid Level Detector (LD3)
- 10. Arterial tube holder
- 11. Venous Pressure Port (P7)
- 12. Venous Level Detector (LD4)
- 13. Plasma Pressure Port (P3)
- 14. Plasma Separator Holder
- 15. Air Detector (AD), Venous Valve (V12), and Blood/Saline Detector (BSD)
- 16. Plasma Inlet Left Valve (V3)
- 17. Plasma Inlet Right Valve (V4)
- 18. Replacement Fluid Left Valve (V5)
- 19. Replacement Fluid Right Valve (V6)
- 20. Adsorption Column Right Holder
- 21. Plasma Outlet Left Valve (V7)
- 22. Plasma Outlet Right Valve (V8)
- 23. Waste Fluid Left Valve (V9)
- 24. Waste Fluid Right Valve (V10)
- 25. Adsorption Column Left Holder
- 26. Plasma Outlet Pressure Port (P6)
- 27. Plasma Outlet tube Holder
- 28. Rinse Valve (V11)
- 29. Plasma outlet chamber holder

## 2.2.4 Blood Pump, Plasma Pump, and Replacement Fluid Pump



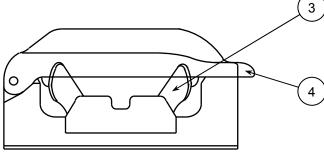


Figure 2.5 Blood Pump, Plasma Pump, and Replacement Fluid Pump

1. Sensor

The sensor detects whether the pump cover is open or closed.

- 2. Rotor
- 3. Tube Clamp

The tube clamp fastens the pump segment.

4. Pump Cover

## 2.2.5 Infusion Pump

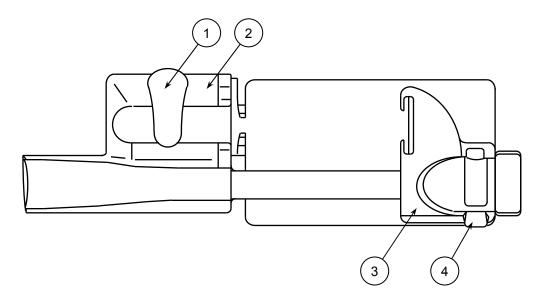


Figure 2.6 Infusion Pump

### 1. Holder Lever

The holder lever secures the syringe.

#### 2. Holder

The flange of the syringe cylinder is set into the holder.

### 3. Syringe Slider

The slider moves the syringe plunger.

#### 4. Unlock Button

While the unlock button is pressed, the syringe slider becomes unlocked and can be moved freely.

## 2.3 Specifications

### 2.3.1 Dimensions and Weight

Dimensions

 Height
 137cm (54.0 inches)

 Width
 44cm (17.3 inches)

 Depth
 34.5cm (13.6 inches)

Floor Space Approximately 47cm (18.5 inches) wide by 59cm

(23.2 inches) deep

■ Weight

Standard system Approximately 77kg (170 lbs.)

# 2.3.2 Electric Safety (Classified According to EN / IEC60601-1)

■ Type of protection against electric shock Class I equipment

Degree of protection against electric shock

Type B Applied part Symbol:



Degree of protection against the ingress of water

Drip proof Symbol: **IPX1** 

■ Degree of safety of application in the presence of a flammable anesthetic mixture with air or with oxygen or nitrous oxide

Not suitable for use

■ Mode of operation

Continuous operation

Type Label

### APHERESIS MACHINE

MODEL : KANEKA MA-03 POWER : 115V~ 50/60Hz 350VA









Distributor

KANEKA Pharma America LLC 546 Fifth Avenue, 21st Floor New York, NY 10036 USA

Manufacturer

NIKKISO CO.,LTD.

20-3, Ebisu 4-Chome, Shibuya-ku, Tokyo 150-6022, Japan 2006-04

SN 66001-01

### 2.3.3 Power Supply

### ■ Voltage

115 V AC 115 V AC  $\pm$ 10 %, 50/60 Hz  $\pm$ 1 Hz

# **MARNING**

Grounding reliability can only be ensured when the machine is connected to an outlet marked "Hospital only" or "Hospital grade".

Never use any adaptor which bypasses the machine ground and the receptacle ground.

Improper or no grounding may cause electric shock.

### **■** Power Consumption (Maximum)

350 VA 5 A

### Battery

Kind Nickel-metal hydride battery (Ni-MH)

Capacity 24 V/1.9 Ah

Storage - Charging of built-in battery

Charge the battery every 6 months in the following procedures,

- 1. Connect the power plug of the machine to the electric outlet.
- 2. Stay the machine power-on for 48 hours.

# NOTICE

If the battery has been completely discharged, the machine cannot be turned on by pressing the POWER ON button in the operation panel.

Then turn the machine on by pushing System-Start Switch in the power supply unit in the right side panel.

## 2.3.4 Fuses (Power Unit)

Nominal voltage	Power line	Heater line	Battery line
115 V AC	F1, T5AH250V	F3, T2AH250V	F5, T1AH250V
	F2, T5AH250V		

F4, Unused

### 2.3.5 Monitoring Parts



The setting values marked "\*" are user changeable.

The alarm range of setting values are shown between parentheses and the lower limit cannot exceed the higher limit.

Limit value is set by every facility.

Variable range is shown between parentheses.

#### **■** Arterial Pressure

Measurement range —300 to +300 mmHg

Measurement accuracy  $\pm 10 \text{ mmHg}$ 

Fixed alarm points Upper limit +200 mmHg\* (0 to +300 mmHg)

Lower limit -170 mmHg\* (-250 to 0 mmHg)

Alarm delay time Maximum 2 seconds

#### **■** Blood Inlet Pressure

Measurement range —200 to +600 mmHg

Measurement accuracy  $\pm 10 \text{ mmHg}$ 

#### **■** Plasma Pressure

Measurement range −200 to +600 mmHg

Measurement accuracy ±10 mmHg

#### ■ Plasma Inlet Pressure

Measurement range —200 to +600 mmHg

Measurement accuracy ±10 mmHg

#### **■** Plasma Outlet Pressure

Measurement range —200 to +600 mmHg

Measurement accuracy  $\pm 10 \text{ mmHg}$ 

#### ■ Replacement Fluid Pressure

Measurement range —200 to +600 mmHg

Measurement accuracy ±10 mmHg

#### **Venous Pressure**

Measurement range -200 to +600 mmHg

Measurement accuracy ±10 mmHg

Auto set alarm range Upper limit +60 mmHg\* (0 to +100 mmHg)

Lower limit -40 mmHg\* (-100 to 0 mmHg)Upper limit +170 mmHg\* (0 to +300 mmHg)

Fixed alarm points (-200 + 100 mmHg)

Lower limit -50 mmHa\*

Alarm delay time Maximum 2 seconds

### Plasma Separator Differential Pressure

-300 to +500 mmHg Measurement range

Measurement accuracy ±10 mmHg

Upper limit +100 mmHg\* Fixed alarm points (0 to Limit value mmHg)

> Lower limit -50 mmHg\* (-150 to 0 mmHg)

Maximum 2 seconds Alarm delay time

#### **TMP**

Measurement range -100 to +500 mmHg

±10 mmHg Measurement accuracy

Fixed alarm points Upper limit +60 mmHg\* (0 to Limit value mmHg)

> Lower limit -50 mmHg\* (-150 to 0 mmHg)

Maximum 2 seconds Alarm delay time



Definition

 $TMP = \left(\frac{P2 + P6}{2}\right) - P3$ P2 = Blood inlet pressure P3 = Plasma pressure

P6 = Plasma outlet pressure (=Blood outlet pressure)

#### **Adsorption Column Differential Pressure**

-300 to +500 mmHg Measurement range

Measurement accuracy ±10 mmHg

Fixed alarm points Upper limit +120 mmHg\* (0 to Limit value mmHg)

> Lower limit \_60 mmHg\* (-150 to 0 mmHg)

Maximum 2 seconds Alarm delay time

### Blood/Saline Detector (Air detector block)

Method Optical

Judge Blood or No blood

#### Air Detector

Method Ultrasonic waves Sensitivity 0.02 mL (bubble)

Blood flow rate: 200 mL/min

0.0003 mL (micro bubble: blood/air mixture)

Blood flow rate: 200 mL/min

#### **■** Blood Leak Detector

Method Optical

Sensitivity 0.25 mL blood/min Hematocrit 32 %

(Standard plasma flow rate: 50 mL/min) 0.4 mL blood/min Hematocrit 32 % (Maximum plasma flow rate: 90 mL/min)

Percentage terms displayed as blood leak data shows approx. 2% attenuation out of 1mL leak while standard

(100%) means no blood leak.

Alarm response Response from the blood leak detector delays to remove

disturbances.

The delayed response depends on the plasma flow rate.

#### **■** Fluid Detector

Method Ultrasonic waves Sensitivity 0.5 mL (bubble)

Fluid flow rate: 200 mL/min

Alarm delay time 2 seconds at a maximum

#### ■ Level Detector

Method Ultrasonic waves

Sensitivity  $\pm 1.0 \text{ mm}$ 

Alarm delay time 2 seconds at a maximum

### ■ Conductivity Detector

Measurement range 0 to 80 mS/cm

Measurement accuracy ±30 % (Temperature of liquid: 15 to 35 °C)
Alarm points ±30 % (Temperature of liquid: 15 to 35 °C)
Lower conductivity (Regeneration solution)

42.0 mS/cm

Lower conductivity (Replacement solution)

11.2 mS/cm

Upper conductivity (Replacement solution)

20.8 mS/cm

Alarm delay time 2 seconds at a maximum

#### 2.3.6 Actuators

### ■ Blood Pump

I.D. 4.0mm O.D 8.0mm Tubing size Setting range 0, 7 to 200 mL/min

Flow rate accuracy Set value  $\pm 5$  % ( $\pm 10$  %, with the following conditions)

Minimum –100 mmHg(-150 mmHg) Inflow pressure

Maximum –30 mmHg(+150mmHg) Minimum +100 mmHg (0 mmHg)

Outlet pressure Maximum +200 mmHg (+500mmHg)

Stoppage of the Blood Pump is automatically

Protection system

monitored.

Rotation (reverse rotation) of the Blood Pump is

automatically monitored.

Blood flow rate = Rotation of the Blood Pump Display method

### Plasma Pump

Outlet pressure

In case of using as the Plasma Pump

Tubing size I.D. 2.7mm O.D 6.7mm Setting range 0. 4 to 90 mL/min

Flow rate accuracy Set value  $\pm 5$  % (  $\pm 10$  %, with the following conditions)

Minimum 0 mmHg(-150 mmHg) Inflow pressure

Maximum +200 mmHg(+250mmHg) Minimum +130 mmHg (0 mmHg) Maximum +240 mmHg (+500mmHg)

Protection system Stoppage of the Plasma Pump is automatically.

Rotation (reverse rotation) of the Plasma Pump is

automatically monitored.

Plasma flow rate = Rotation of the Plasma Pump Display method

#### Replacement Fluid Pump

When PA2 is selected

I.D. 2.7mm O.D 6.7mm Tubing size

Setting range 0, 4 to 90 mL/min

Flow rate accuracy Set value  $\pm 5$  % (  $\pm 10$  %, with the following conditions)

Minimum 0 mmHg Inflow pressure Maximum +80 mmHg

Minimum 0 mmHg (-50 mmHg)

Outlet pressure Maximum +50 mmHg (+500mmHg)

Protection system Stoppage of the Replacement Fluid Pump is

automatically monitored.

Rotation (reverse rotation) of the Replacement Fluid

Pump is automatically monitored.

Display method Replacement fluid flow rate = Rotation of the

Replacement Fluid Pump

### ■ Infusion Pump

Setting range 0.0 to 10.0 mL/h
Outlet rate accuracy 7 % of setting value

Back pressure +500 mmHg

Type of syringe 20 mL disposable syringe (luer lock)

Bolus process 1500 mL/h Total flow measurement range 0 to 99.9 mL

Total flow measurement accuracy ±10 %

Protection system Stoppage of the Infusion Pump is automatically

monitored.

Reverse movement of the Infusion Pump is

automatically monitored.

#### ■ Blood Warmer

Setting range 35.0 to 39.0 °C Measurement range 10.0 to 50.0 °C

Measurement accuracy Measurement value ±0.8 °C

Blood flow rate: 100mL/min, at a constant ambient

temperature

Alarm point Upper limit 41 °C

## 2.4 Disposable Parts

# **⚠** CAUTION

- 1. Only use disposable parts that are approved.
- 2. Disposables (blood tube sets, plasma separators, syringes, etc.) are to be disposed of according to the applicable laws and regulations.

### Use following disposable parts.



Disposables should be used in accordance with the instructions provided in the Instruction for Use of each device.

### 2.4.1 Adsorption Column

### PA2

• LIPOSORBER® LA-15

# **⚠** CAUTION

The method for Rinsing, Priming and/or Treatment depends on the model/type of the disposables. Confirm that each product can be applicable to the machine by consulting the Instruction for Use of each device.

### 2.4.2 Blood Tubing

Tubing System for Plasmapheresis (NK-M3R(U))

### 2.4.3 Plasma Separator

SULFLUX® KP-05 Plasma Separator

## 2.4.4 Syringe for Infusion Pump

20mL Syringe (luer lock)



Only use a 20mL luer lock listed above. Use of unapproved syringes may cause inaccurate heparin infusion.

### 2.5 Environmental Issues



Properly dispose of all disposables and other device components according to facility and local governing ordinances.

The MA-03 contains the following materials listed below.

#### Metals

- Stainless steel
- Aluminum
- Copper
- Iron
- Brass

#### Plastics

- Polycarbonate (PC)
- Polysulfone (PSU)
- Polyamide (PA)
- Polyoxymethylene (POM)
- Polyvinyl Chloride (PVC)
- Polyurethane Rubber (PUR)
- Monomer-Cast Nylon (UMC)
- Acrylonitrile-Butadiene-Styrene (ABS)
- Acrylonitrile-Styrene-Acrylate (ASA)

#### Other Materials

- Electronic components, such as LCD and P.C.B.
- Glass, Ceramic
- Nickel-Metal Hydride Battery (Ni-MH battery)

### 2. OVERVIEW

## 3. TREATMENT METHOD OF THE MA-03

## 3.1 Applicable Treatment

The MA-03 is applicable for LDL-C plasma adsorption treatment.

### ■ Plasma Adsorption Treatment

The blood withdrawn from the patient is separated into plasma and blood cells by passing through the membrane type plasma separator. Plasma is led to the adsorption column where specific substances are adsorbed and removed.



## 3.2 Plasma Adsorption Treatment

### 3.2.1 Overview of PA2

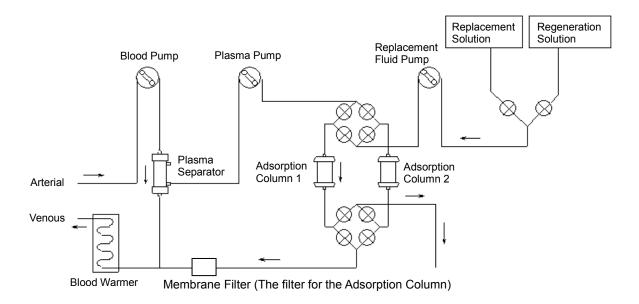


Figure 3.1 PA2

- 1. The blood which is withdrawn by the Blood Pump passes the Plasma Separator, and that is separated into blood cells and plasma.
- 2. Passing the Adsorption Column 1 where specific substance is adsorbed and removed, plasma joins the blood cells and return to the patient via Venous Access.
- 3. After the preset volume of plasma is processed in the Adsorption Column 1, the path of plasma is automatically switched to the Adsorption Column 2.
- 4. While plasma is processed in the Adsorption Column 2, the Adsorption Column 1 is regenerated.
- 5. Thus the two adsorption columns repeat adsorption and regeneration, to keep treatment until target volume of plasma is processed.



#### Regeneration:

The specific substance is flushed with the exclusive regeneration fluid from the adsorption column. Regeneration fluid is replaced with replacement fluid and the column is recovered to the usable state.

## 3.2.2 Action of PA2

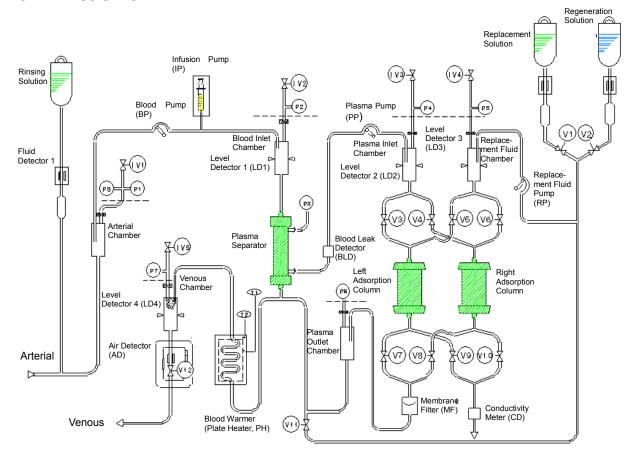
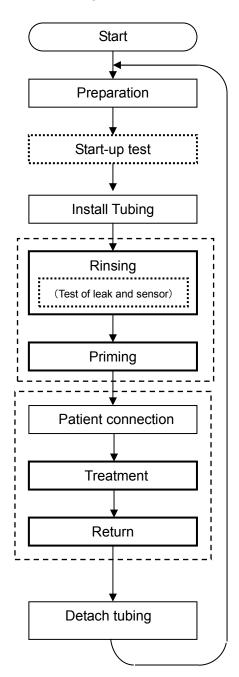


Figure 3.2 PA2

- (1) Blood is withdrawn from the patient by the Blood Pump (BP) through the Arterial Chamber. The withdrawn blood is led to the Plasma Separator through Blood Inlet Chamber with-anticoagulant which is infused by the Infusion Pump (IP).
- (2) The blood in the Plasma Separator is separated into blood cells and plasma, and plasma is led to the Left Adsorption Column by the Plasma Pump (PP) through the Blood Leak Detector (BLD) and the Plasma Inlet Chamber.
- (3) The specific substance contained in plasma is adsorbed in the Left Adsorption Column and removed. Plasma is led to the Membrane Filter (MF) and the Plasma Outlet Chamber, and mixed with the blood cells, which has been separated by the Plasma Separator.
- (4) The mixed blood is warmed up to proper temperature in the Blood Warmer (PH), and is returned to the patient through the Venous Chamber and the Air Detector (AD).
- (5) After the preset volume of plasma is processed in the Left Adsorption Column, the flow path of plasma is changed by the Plasma Inlet Left Valve (V3), the Plasma Inlet Right Valve (V4) and the Plasma Outlet Left Valve (V7), and the Plasma Outlet Right Valve (V8). Plasma is led to the Right Adsorption Column, and the adsorption process continues.
- (6) While plasma is processed in the Right Column, plasma in the Left Column is flushed out with Replacement Fluid, which is led to the column by the Replacement Fluid Pump (RP). The flow path is changed by the Replacement Fluid Valve (V1) and the Regeneration Fluid Valve (V2) to lead regeneration fluid, with which the specific substance is flushed out. And the Adsorption Column recovers to usable state. Then, the flow path is changed again by the Replacement Fluid Valve (V1) and the Regeneration Fluid Valve (V2) to lead Replacement Fluid, with which Regeneration Fluid is Replaced. This series of process is called regeneration process.
- (7) After the preset quantity of plasma in the Right Adsorption Column is processed, the flow path is changed by the plasma Inlet Left Valve (V3), the Plasma Inlet Right Valve (V4) and the Plasma Outlet Left Valve (V7), and the Plasma Outlet Right Valve (V8), plasma is led to the Left Adsorption Column where the adsorption process continues.
- (8) As mentioned above, each Adsorption Column alternates adsorption and regeneration process, and performs treatment.

## 3.3 Operation Flow

Here is the general flow of operation.



Check all disposables necessary for the procedure and collect them.

The safety functions of the MA-03 are checked before the treatment starts.

Install the tubing and disposables to the MA-03.

The tubing and disposables are rinsed with rinsing solution.

(Safety function of the machine, leak of the tube etc. are confirmed before the treatment starts.)

The tubing system and disposables are primed with heparinized priming solution.

Patient is connected to the extracorporeal circuit through the arterial and venous lines.

Apheresis is performed.

Arterial line is disconnected from the patient and connected to Return solution.

Blood and plasma in the extracorporeal circuit are returned to the patient.

The tubing system and disposables are removed from the MA-03 and properly discarded.

Figure 3.3 Operation Flow (Conceptual Diagram)



Once the current process step completes, the step of the machine can be forwarded to the next process, and can not return to the previous process step.

#### 3. TREATMENT METHOD

## 4. DISPLAY SCREEN OF THE MA-03

### 4.1 Screen Section

Generally the MA-03 can be operated interactively. While selecting various keys displayed on the screen, operation can be advanced.

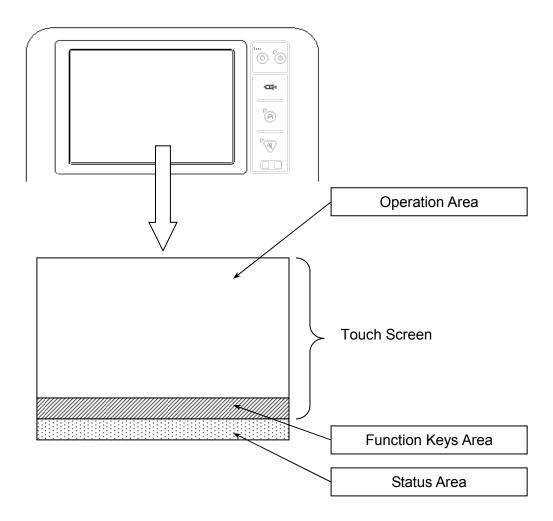


Figure 4.1 Screen Section



Do not press buttons and keys with a ballpoint pen or other sharp pointed object. This may damage the MA-03 machine.

## 4.2 Operation Area

Several keys appear in the "Operation Area", according to the mode and operating status.

### 4.2.1 Main Keys in "Operation Area"

### ■ Screen Operation Keys

Back displays the previous screen.

Yes displays the next screen after executing the selected mode or order.

No displays the next or previous screen after canceling the selected mode or order.

Help displays guidance related to the alarm.

#### ■ Mode Selection Keys

Install leads to the process to install the blood tubing tubing. leads to the process to rinse and priming the blood tubing. Rinsing/ Priming leads to the process to re-priming the blood tubing. Re-priming Treatment/ leads to the process to perform the treatment and to return the blood Return to the patient after treatment. Re-return leads to the process to re-return the blood to the patient. leads to the process to detach the blood tubing. Detach When the key is touched, the window to confirm the termination of tubing treatment appears.

# **WARNING**

After activating the "Detach tubing" process, the machine can no longer return to the previous process.

This key is accepted in any process from the "Procedure" screen. Do not operate this key unless the complete termination of the treatment is intended and the patient is disconnected.

### **■** Function Instruction Keys

Cancel treatment

This key is to intentionally terminate a process of Rinsing, Priming, Treatment or Return.

When the key is touched, the window to confirm the termination of treatment appears.

## **A** WARNING

Once the "Cancel Treatment" is executed, both Treatment and Return processes are disenabled to continue or execute. Do not operate this key unless a premature termination of the treatment is intended.

Continue

resumes the operation which has been suspended by the alarm.

## 4.2.2 Operational State Screen

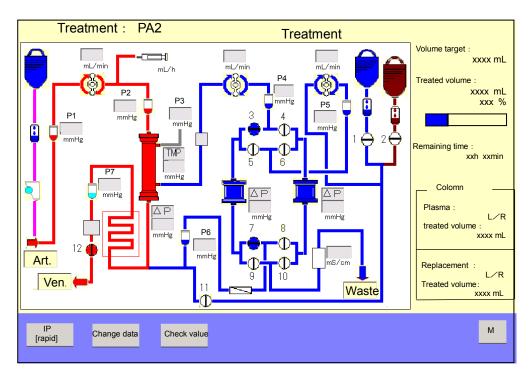


Figure 4.2: Operational State Screen

## 4.3 Function Keys Area

Function keys are displayed in the function key area, according to the operational state and mode.

The Infusion Pump works faster only when continually pressed.

Change. data

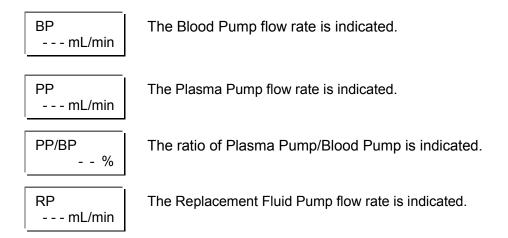
displays the screen to change setting data.

Check value

displays the screen for checking the monitoring value.

### 4.4 Status Area

The information is indicated in the status area, according to the operational state and mode.



## 5. DATA SETTING OF THE MA-03

## **5.1 Basic Setting Procedure**

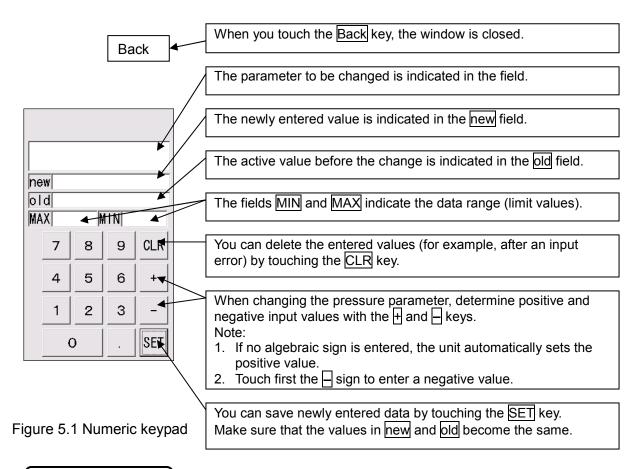
There are two ways to input or change setting values:

- 1. Input of data by using the numeric keypad
- 2. Direct change of data by turning the flow rate knob.

### 5.1.1 Numeric keypad

When you touch the data field (parameter display) which you are to change, a new screen with a numeric keypad for data input automatically appears on the screen.

By touching the appropriate key, the following functions can be executed:



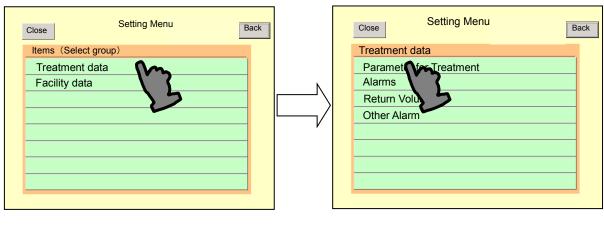


Before any treatment starts, make sure the value which is input by the numeric keypad is the same as the number in the field.

## **5.1.2 Basic Methods of Data Input**

The basic methods for data input described below is applicable to almost all data changes.

With the Data fields and keys that are specially marked by the green frame, direct change can be made.



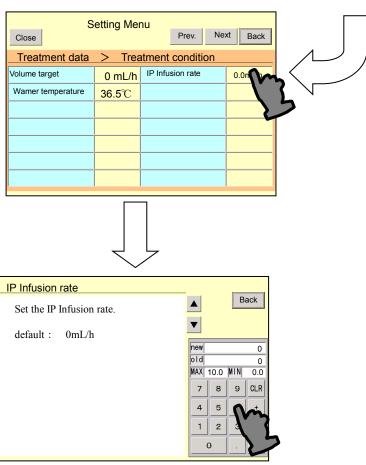


Figure 5.2 Basic Methods of Data Input

Data input/data change by example of "IP Infusion rate":

- 1. Touch the Change data key on the function key area.
- 2. Touch the Treatment data key on the "Items (Select group)" of "Setting Menu" Screen.
- 3. Touch the numeric field to the right of IP Infusion rate.
- 4. The numeric keypad will appear on the display.
- 5. Enter the required value on the numeric keypad by touching the corresponding keys. The entered value appears in the <a href="new">new</a> field.

  If the entered value is incorrect, delete the value with the <a href="CLR">CLR</a> key.
- 6. Touch the <u>SET</u> key to save the entered value. The newly stored value appears in the <u>old</u> field.



After entering a new value, make sure that the values in the new and old fields are the same.

### 5.2 Data List

## 5.2.1 Treatment data setup

An operator usually set three values of "Parameter for Treatment" before starting Treatment process.

Contents	Default value	Setting range	Unit			
Parameter for Treatment						
Volume target	0	0 ~ 20,000	mL			
IP Infusion rate	0.0	0.0 ~ 10.0	mL/h			
Blood warmer temperature	36.5	35.0 ~ 39.0	°C			
Alarms						
Arterial pressure (upper)	200	0 ~ 300	mmHg			
Arterial pressure (lower)	-170	-250 ~ 0	mmHg			
Venous pressure (upper)	170	0 ~ 300	mmHg			
Venous pressure (lower)	-50	-200 ~ 100	mmHg			
Venous pressure (Auto-upper)	60	0 ~ 100	mmHg			
Venous pressure (Auto-lower)	-40	-100 ~ 0	mmHg			
Limit value of Venous pressure alarm (Auto-lower)	10	-100 ~ 100	mmHg			
Return volume						
Blood volume in Separator	100	0 ~ 200	mL			
Plasma volume	250	0 ~ 500	mL			
Blood volume after Plasma is returned	50	0 ~ 200	mL			
Re-Return volume (Blood only)	0	0 ~ 999	mL			
Other alarm						
Separator differential pressure (upper)	100	0 ~ Limit value	mmHg			
Separator differential pressure (lower)	-50	-150 ~ 0 mmHg				
TMP (upper)	60	0 ~ Limit value mmHg				
TMP (lower)	-50	-150 ~ 0 mmHg				
Column differential pressure (upper)	120	20 0 ~ Limit value mmHg				
Column differential pressure (lower)	-60	0 -150 ~ 0 mmHg				



An operator must enter double-figures passwords to set the "Limit value of Venous pressure alarm (Auto-lower)", and is responsible for it.



A responsible person should set the three "Limit values" in Maintenance mode.

## 5.2.2 Facility data setup

# **A**CAUTION

An operator must enter double-figures password to set each "Facility data setup" value, and is responsible for it

Contents	Default value	Setting range	Unit			
Parameter for Facility						
Syringe calibration	20.2	14.0 ~ 24.0	mm			
Parameter for Blood flow monitor						
Insufficient Blood flow (flow rate)	20	7 ~ 40	mL/min			
Insufficient Blood flow (time)	30	0 ~ 60	sec			
BP flow limit (start/flow)	20	10 ~ 40	mL/min			
BP flow limit (start/pressure)	-70	-100 ~ -30	mmHg			
Parameter for Blood Leak Detector						
BLD alarm point	5.0	1.0 ~ 5.0	mL/L			
BLD 2nd. calibration	0 (invalid)	0 ~ 1	-			
BLD 2nd. calibration execute time	100	0 ~ 200	mL			
Sensor Valid/Invalid						
LD2 detection	0 (invalid)	0 ~ 1	-			
LD3 detection	0 (invalid)	0~1	-			
FD1 detection	1 (valid)	0 ~ 1	-			



Setting values should be within the setting range shown in the list above, and the lower limit cannot exceed the higher limit.

#### 5. DATA SETTING

## 6. TREATMENT OPERATION OF THE MA-03

This chapter provides the qualified operator with the recommended daily procedures to operate the MA-03 for regular treatment.

To operate the MA-03 for the Plasma Adsorption treatment see chapter "2. OVERVIEW".

## **6.1 Machine Preparation**

After the MA-03 is installed and preparation procedure is about to start, make sure:

- There is no deformation of the machine.
- ✓ The power cord is connected to outlet with ground terminal.
- ✓ The manual handle for the blood pump is available.

## 6.1.1 Turning on the Machine

1. Press the "POWER ON" button. (See Figure 6.1)

The green indicator lamp lights, and the "Initial" screen will appear on the LCD. (See Figure 6.2)

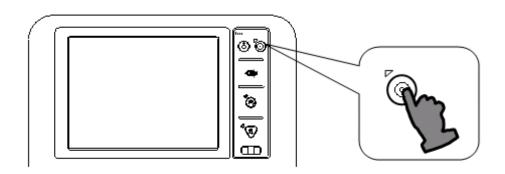


Figure 6.1 POWER ON Button on the Monitor/Operation Panel



When another treatment operation is intended, please once turn off the power and wait for more than 30 minutes, or the internal temperature may rise to generate an alarm.

### 6.1.2 Testing the Machine



Prior to the first treatment of the day, the machine performs the Start-up test to ensure its proper function.



Figure 6.2 Initial Screen

1. Touch the Start preparation key on the "Initial" screen.

The "Confirmation" screen will appear on the LCD.

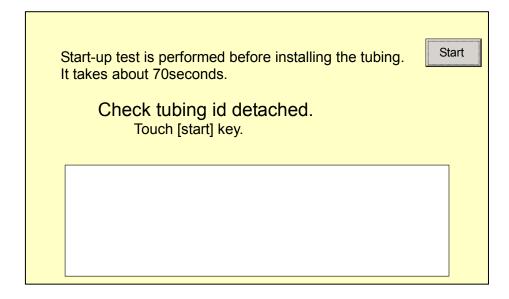


Figure 6.3 Confirmation Screen

2. Touch the Start key on the "Confirmation" screen.

The "Start-up Test" screen will appear on the LCD.

Buzzer test:

After you touch the Start key, confirm the alarm function by hearing the buzzer sound.



If the buzzer does not sound during the Start-up test, the buzzer will not sound during treatment.

In this case, do not start any treatment.

Start-up test running					
Remaining time: 70 sec  Confirm the Buzzer sounding.  CPU test [ OK ] Pump test [Waiting]  RAM test [Running] Valve test [Waiting]					
ROM test 3PRAM test Check data	[Waiting] [Waiting]	Transducer test US Sensor test Thermistor test	[Waiting] [Waiting] [Waiting]		
Shook data	[**************************************	Conductivity test	[Waiting]		

Figure 6.4 Start-up Test Screen

#### 6. TREATMENT OPERATION

3. The "Result of Start-up test" screen appears in the LCD when any defect or abnormality is found in the Start-up test.

Execute one of the followings by touching the Confirm key according to the guidance in the screen;

- (1) Repeat the "Start-up test",
- (2) Cancel the operation.

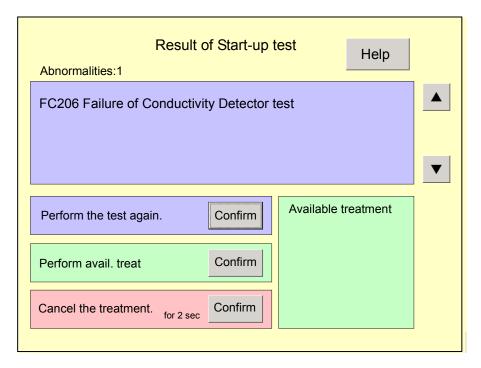


Figure 6.5 Result of Start-up Test Screen



If the machine fails the Start-up test, do not use this machine for any treatment. Contact the service person.



"Perform avail. treat" function is not available.

## **6.1.3 Selecting the Treatment Method**

After the self test completes, the "Treatment Selection 1" screen will appear on the LCD.
 Touch the key you selected.

After the key is touched, the color of the key becomes blue.

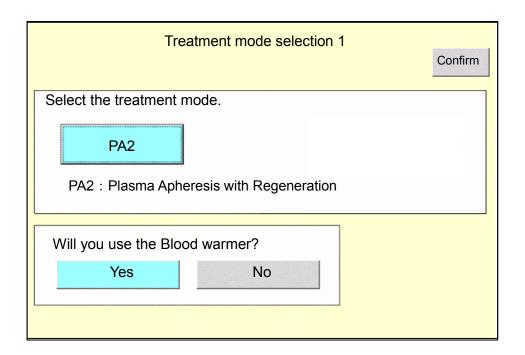


Figure 6.6 Treatment Selection 1 Screen

- Touch the key to use/not use the blood warmer on the "Treatment Selection 1" screen.
   After the key is touched, the color of the key becomes blue.
- 3. Touch the Confirm key on the "Treatment Selection 1" screen.

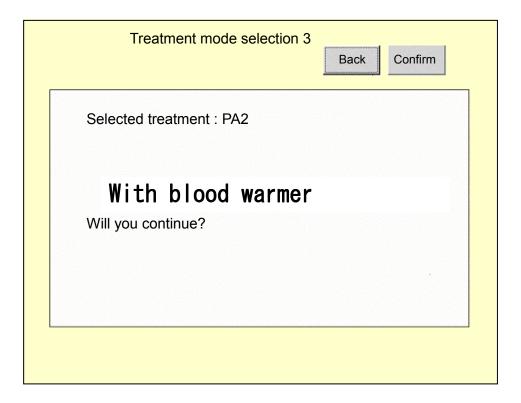


Figure 6.7 Treatment Selection3 Screen

4. Confirm the selected treatment method is displayed on the "Treatment Selection 3" screen, and touch the Confirm key.

The "Selection of Data Logging" screen appears. Close the "Selection of Data Logging" screen and the "Procedure" screen appears.



See Section 8.3.4 Data Logging for the details.

### 6.2 PA2

### 6.2.1 Install Tubing



Line map of the blood tubing for PA2 mode is directly printed on the machine surface.

1. The red lines show the blood flow.

The following shows major fluid path.

- 2. The yellow lines show the plasma flow.
- 3. The blue lines show the replacement fluid flow.
- 4. The brown lines show the regeneration fluid flow.
- 1. Touch the Install tubing key on the "Procedure" screen.

The "Install tubing" screen will appear on the LCD.

Each valve opens automatically to install the tubing.

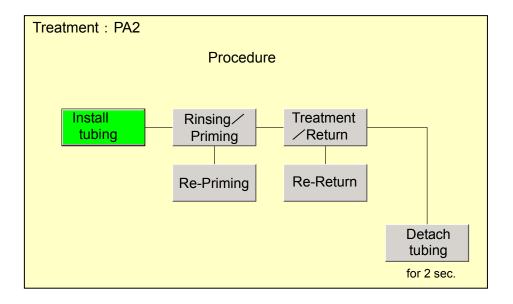


Figure 6.8 Procedure Screen

## **MARNING**

Once moved into Detach tubing process by touching the Detach tubing key, the machine can no longer return to the previous process.

This key is accepted in any process from the "Procedure" screen. Do not operate this key unless the complete termination of the treatment is intended.

#### 6. TREATMENT OPERATION

2. Install the tubing referring to the tubing diagram displayed on the "Install tubing" screen on the LCD.

To confirm the tube is properly installed, see the Figure 6.9 / 6.10 (The provided figure depends on the configuration of the MA-03.)



Confirm all connection points of blood tubing are aseptic (capped) before use.

This operation should be performed aseptically.

## **MARNING**

Do not touch the fluid in the waste container to prevent contamination.

# **⚠** CAUTION

While installing the tubing (Install tubing Screen is displayed), install the tubing only and make sure the Separator and Column are not attached. If the Separator or Column is attached, alarm will occur during the Rinsing/Priming process.

# **⚠** CAUTION

Do not stay on the <code>[install tubing]</code> screen for Attach <code>[tubing only]</code> for more than 30 minutes, or the internal temperature may rise to generate an alarm.

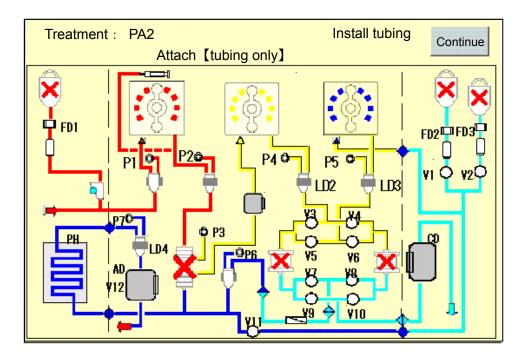


Figure 6.9 Install Tubing Screen for PA2

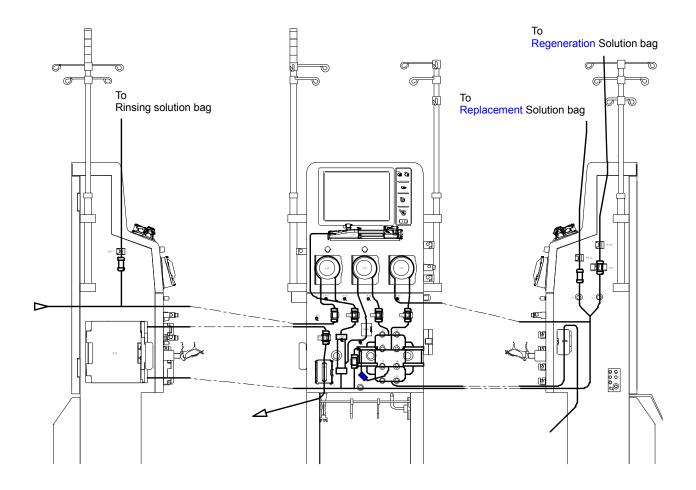


Figure 6.10 Configuration of tubing, Separator and column for PA2.

- 3. Install the pump-tube segment to each pump.
  - 1) Open the pump cover.
  - 2) Place the inlet of the pump-tube segment to the left side.
  - 3) Insert the tube between the pump rotor and stator by turning the rotor clockwise.
  - 4) Place the outlet of the pump-tube segment to the right side and close the pump cover.



Be careful not to pinch your fingers between the rotor and the stator.

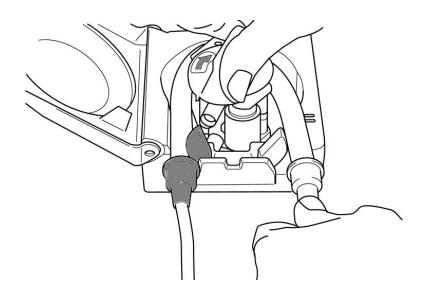


Figure 6.11 Inserting the Pump-tube Segment

# **A**CAUTION

Make sure the collar of the Pump-tube segment is positioned below the bottom of the tube clamp.

This will prevent kinking of the Pump-tube segment during the pump operation.

4. Open the Level Detector door and place each chamber into each holder and shut it with a snap.

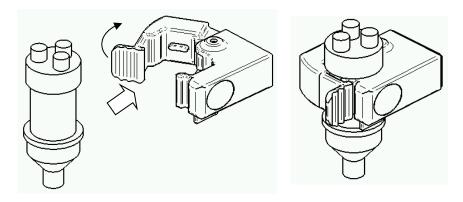


Figure 6.12 Installing the Chamber to the Level Detector

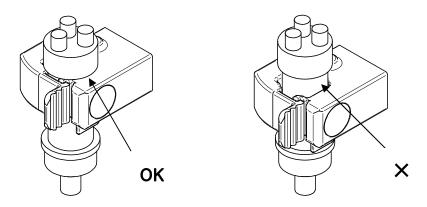


Figure 6.13 Position of the chamber

5. Open the Fluid Detector door and place each tube into each holder and shut it with a snap.

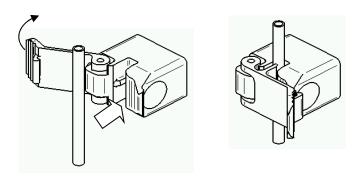


Figure 6.14 Installing the Tube to the Fluid Detector

- 6. Place the chamber into the Drip Detector.
- 7. Place each chamber into each chamber holder.
- 8. Open the Conductivity Detector door and place the detects-conductivity tube segment into the holder and shut it with a snap.

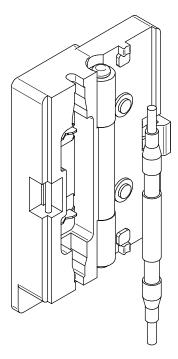


Figure 6.15 Installing the detects-conductivity tube segment into the Conductivity Detector

9. Open the Blood Leak Detector door and place the tube into the holder and shut it with a snap.

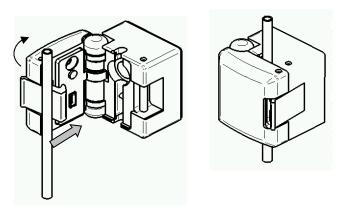


Figure 6.16 Installing the Tube to the Blood Leak Detector

10. Open the Air Detector door and place the tube into the holder and shut it with a snap.

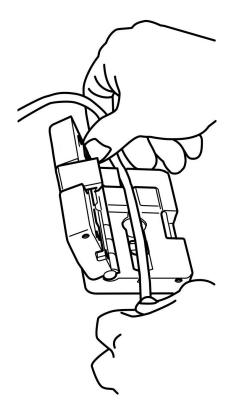


Figure 6.17 Installing the Tube to the Air Detector

- 11. Install each tube into each Valve.
  - 1) Press the holder of the Valve.
  - 2) Place the tube at the center of the Valve.
  - 3) Make sure the holder closes firmly.

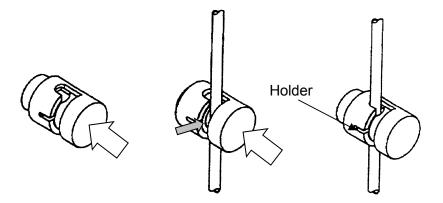


Figure 6.18 Installing the Tube to the Valve

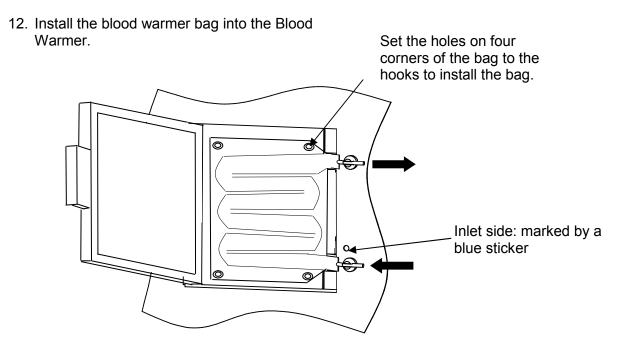


Figure 6.19 Installing the Bag to the Blood Warmer



When closing the cover of blood warmer, be careful not to pinch or bend the bag and tubes.

Place the tube in the tube holder correctly to prevent kink and blockage.

13. Connect the transducer Protective Filter to each pressure port by turning them clockwise.

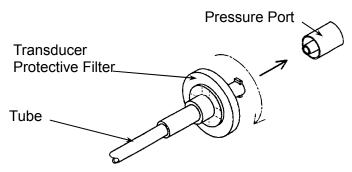


Figure 6.20 Attach the Transducer Protective Filter

# **MARNING**

If any of the external Transducer Protective Filter, internal Transducer Protective Filter or the internal transducer is bloodstained, the filter must be replaced to new one. And the transducer and the adjacent parts must be disinfected or replaced. The internal parts of machine should be exchanged or disinfected only by the person authorized by DISTRIBUTER.

#### 6. TREATMENT OPERATION

- 14. Connect the tube to the syringe, and attach the syringe to the Infusion Pump.
  - 1) Fill the syringe with heparin solution under the instructions of the physician.
  - 2) Move the slider while pressing the unlock button of the slider.
  - 3) Connect the tube of the heparin line to the syringe.
  - 4) Set the syringe into the syringe holder, by fitting the syringe collars into the channels of the holder and slider.
  - 5) Pull up the holder lever, and turn it and release it on the syringe.



Figure 6.21 Installing the Syringe to the Infusion Pump



Clamp the syringe line with a forceps in case that the tubing is not connected with a syringe before the Rinsing process is executed, or the "Leak error" alarm may occur in Rinsing process.

15. Touch the Continue key on the "Install tubing" screen.

All valves close automatically and the "Attach Disposable" screen will appear on the LCD.

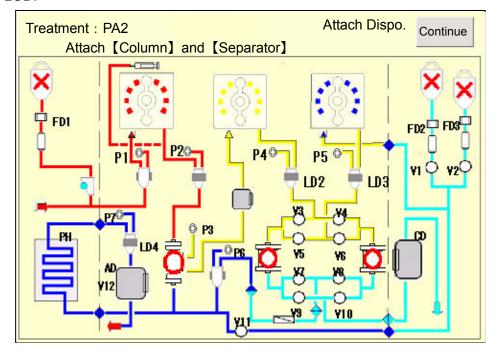


Figure 6.22 Attach Disposable Screen for PA2

- 16. Attach the separator and columns to the holders respectively.
- 17. Connect the blood tubing to the separator and columns.

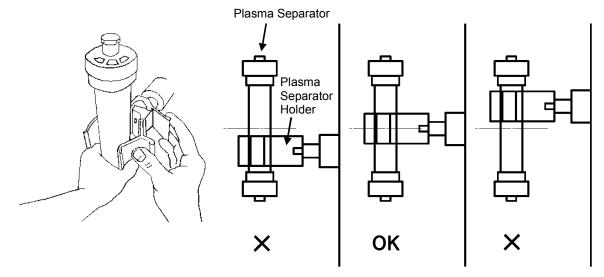


Figure 6.23 Attach the separator



While connecting tubing lines to other disposables, a careful handling is required not to spill out liquid from them.

Hold the middle or upper part of plasma separator by the holder as shown in figure 6.23. Otherwise "Span test error for P3 or P6" alarm may possibly be generated in the Rinsing process.

### 6.2.2 Rinsing and Priming

1. Touch the Continue key on the "Attach Disposable" screen.

The "Procedure" screen will appear on the LCD.

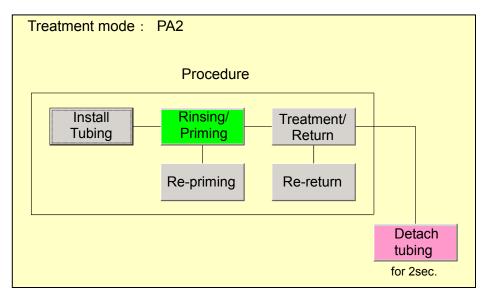


Figure 6.24 Procedure Screen



Once moved into Detach tubing process by touching the Detach tubing key, the machine can no longer return to the previous process.

This key is accepted in any process from the "Procedure" screen. Do not operate this key unless the complete termination of the treatment is intended.

# NOTICE

In case any improper installing of tubing line (e.g., a line is not installed in the valve) is found after the completion of Install Tubing process, touch the <a href="Install Tubing">Install Tubing</a> key and the "Re-install Tubing" screen appears.

On the "Install Tubing" screen, any desired valve can open with touching the corresponding valve marking on the screen, then re-install the tubing line properly.

Touch the Rinsing/Priming key on the "Procedure" screen.
 The "Preparation of Rinsing" screen will appear on the LCD.

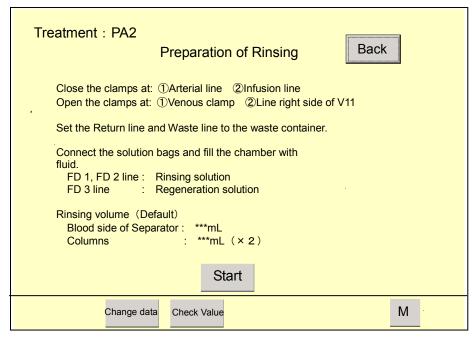


Figure 6.25 Preparation of Rinsing Screen

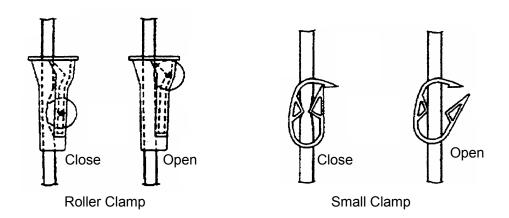


Figure 6.26 Roller Clamp and Small Clamp

- 3. Close the clamps on the arterial and infusion lines.
- 4. Open the clamps on the venous line and on the line right of V11.
- 5. Put the end of the venous and waste lines to the waste container.

# **⚠** CAUTION

Waste bags, if used, shall be hung on the hooks equipped above the Waste Fluid Container Table.

If a waste bag is placed above the valve V1, the automatic fluid level adjustment of drip chamber may not function correctly in Rinsing process.

## **A**CAUTION

In case the end of the waste line is placed closer to the floor (e.g., at closer to the bottom of the waste container), the "Column differential press.(lower)" alarm might occur.

- Hang each solution bag on each bag hanger.
- 7. Connect each tubing to each solution bag.
- 8. Fill each drip chamber on each infusion line about 1/2 by squeezing and releasing them.



To close a Roller Clamp, lower the roller to the end. If the roller stays halfway, leak may occur.

9. Touch the Start key on the "Procedure" screen.

The "Rinsing of Arterial Line" screen will appear on the LCD.

Treatment: PA2

Rinsing

Open clamps of the infusion and arterial lines.

Fill the arterial line with the saline to remove air in the line.

Close the clamp of the arterial line.

Continue

Figure 6.27 Rinsing of Arterial Line Screen.

- 10. Rinsing the arterial line manually.
  - Open the roller clamp and the small clamp on both the infusion and arterial lines, and unclamp the arterial line. Rinse the arterial line manually with rinsing solution for about 30 seconds.
  - 2) After filling the arterial line with rinsing solution, clamp the end of the arterial line with forceps.
- 11. Touch the Continue key on the "Rinsing of Arterial Line" screen.

The "Rinsing" screen will appear on the LCD.

The rinsing process starts automatically.

(Leak check starts during the rinsing process.)

Each pump starts at the fixed flow rate.

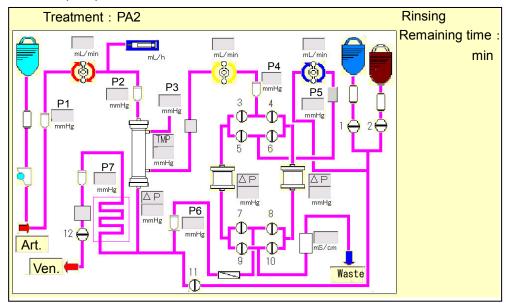


Figure 6.28 Rinsing Screen



In case any improper installing of tubing line (e.g., a tube is not properly installed in the valve) is found during Rinsing process;

- ①Press the BLOOD PUMP Button on the Operation Panel, and the machine becomes into the "Process is suspended" status. (The "Process is suspended" screen appears.)
- ②Touch the Re-install tubing key on the "Process is suspended" screen, and the "Re-install Tubing" screen appears.
- ③Touch any desired valve marking on the "Re-install Tubing" screen to open the corresponding valve opens, then, install the tubing line in the valve properly.
- (4) Confirm the tubing line is properly installed and press BLOOD PUMP Button (a) to resume Rinsing process.

During alarm generating, the install tubing key is invalid.

It becomes effective after reset alarms.

Release all alarms to reactivate the install tubing key.

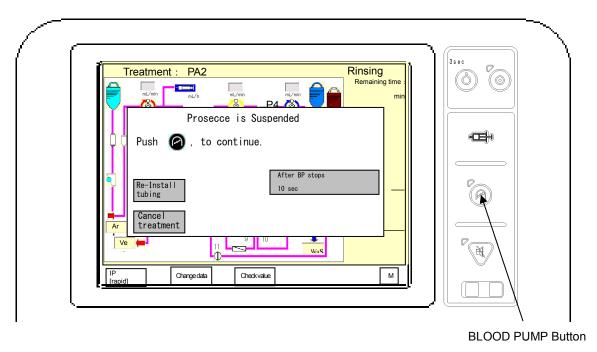


Figure 6.29 Blood PUMP BUTTON on the Operation Panel

12. When the rinsing volume reaches the preset value, each pump stops automatically.
The Preparation of "Priming" screen will appear on the LCD.

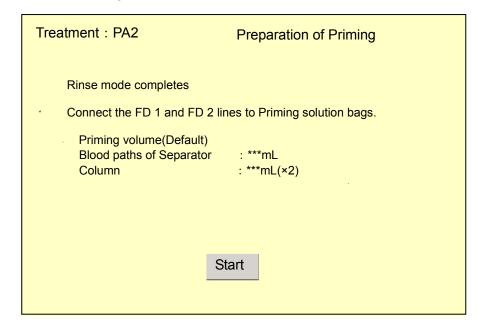


Figure 6.30 Preparation of Priming Screen

Replace rinsing solution bag to priming solution bag and touch the Start key.

The same screen as Figure 6.28 appears and Priming starts. ("Priming" screen)

13. When the priming volume reaches the preset value, each pump stops automatically.

The "Priming Completes" screen will appear on the LCD.

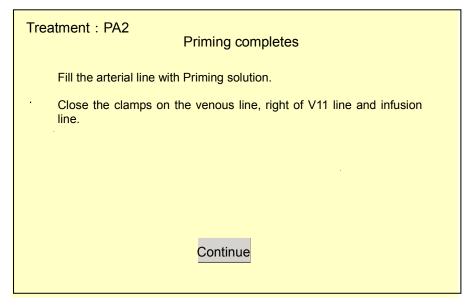


Figure 6.31 Priming completes Screen

Fill the arterial line with saline, and close the clamps on the venous and infusion line and on the line right of V11

Touch the Continue key and the "Procedure" screen appears.

The Re-Priming key appears in yellow color in the "Procedure" screen after the completion of the priming process. Touch the Re-Priming key to execute the re-priming. The device is re-primed with the same volume of priming solution as for the priming.



The MA-03 performs some of the self test during the rinsing and priming process. Depending on the result of the test, some treatment may not be started.



If the machine is turned off while any screen other than the "Procedure" screen (i.e.,

"Rinsing", "Treatment") is displayed, the machine will be in the suspended mode when turned back on, as indicated by the "Process is suspended" screen.

To resume the process, move out of the suspended status by pressing the BLOOD PUMP Button on the operation panel. (See section 6.2.3.5 for the "Process is suspended" screen)

# **⚠** WARNING

The <u>Cancel Treatment</u> key on the "Process is suspended" screen is to intentionally terminate the process before the completion.

When this key is touched and the "Procedure" screen appears, no other key than Detach tubing key can be accepted, that is, it means the termination of whole treatment process. Never touch this key except for the case that the premature treatment-termination is intended.

#### 6.2.3 Treatment



This section shows the procedure from connection of the tubing to a patient to disconnection of the tubing after completing treatment.

Operate under the instructions of the physician.

# 6.2.3.1 Entering the treatment data



Before starting any treatment, check the setting data for treatment on the Preparation of Treatment Screen.

# NOTICE

When the treatment completes, volume target and IP Infusion rate automatically return to the default value (0).

1. Touch the Treatment/Return key on the "Procedure" screen. The Preparation of "Treatment" screen will appear on the LCD.

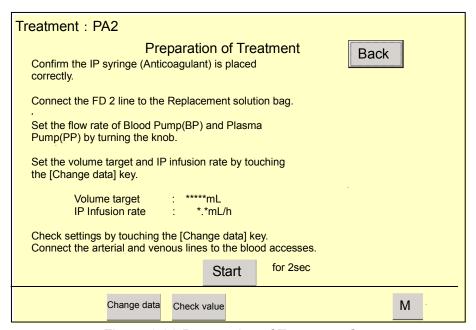


Figure 6.32 Preparation of Treatment Screen

- 2. Set the blood flow rate of the Blood Pump (BP) by turning the knob.
- 3. Set the fluid flow rate of the Plasma Pump (PP) and the Replacement Fluid Pump (RP) by turning the knob of Plasma/Replacement ratio.
  - Set the plasma flow rate as a percentage of the blood flow rate.
  - The replacement fluid rate should be the same as the plasma flow rate.
- 4. Touch the Change data key on the "Treatment" screen.
  - The "Setting Menu" screen will appear on the LCD.
  - See chapter 5 for setting the data.

# 6.2.3.2 Connection to the patient

1. After making sure the roller clamp and the small clamp on the infusion line closes, clamp the arterial and venous lines with forceps.

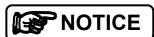
# **A**CAUTION

- 1. Confirm that the tubing and solution bags are correctly installed and connected.
- Confirm that no bubble remains in the tubing.
- 3. If any bubbles remain, tap the tube and move the bubbles to the upper part of the chamber.
- 4. Confirm that the chambers are properly filled and the transducer protective filters are not wet.
- Close the clamps on the cannula.Cannulate the patient under the instructions of the physician.
- 3. Aseptically connect one cannula to the arterial line.
- 4. Aseptically connect another cannula to the venous line.
- 5. Open the clamps on all lines except on the infusion line and on the right side of V11.
- 6. Touch the Start key on the Preparation of "Treatment" screen.

The "Treatment" screen will appear on the LCD.

# 6.2.3.3 Starting the treatment

1. The pump starts moving.



During the treatment, monitor the following:

- 1. Condition of the patient.
- 2. Operation of the machine.
- 3. No blood leak from the connected parts of the tubing, Separator and Adsorption Column(s).

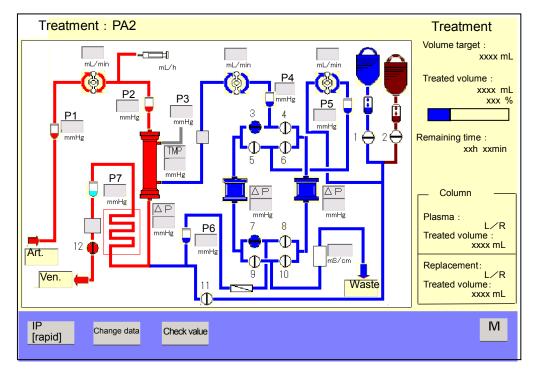


Figure 6.33 Treatment Screen

# 6.2.3.4 Monitoring the treatment

The "Check Value" screen of the MA-03 helps monitor the general status of treatment.

1. Touch the Check value key on the "Treatment" screen.

"Check" Value screen will appear on the LCD.

# 6.2.3.5 Power Failure during Treatment

In case of a power failure, all pumps stop, all valves close, and all detectors become inactive.

Alarm buzzer sounds uninterruptedly for two minutes and more, which cannot be stopped with the MUTE Button.

When main power returns, the machine becomes automatically in "Process is suspended" status (The "Process is suspended" screen appears). All pumps keep stop and all valves keep closed. To resume the treatment, push the button in the right side of the operation panel.



To stop the buzzer, keep pressing the POWER OFF Button in the right side of the operation panel for at least 3 seconds.

In this condition, even when the commercial power supply returns, the MA-03 remains power OFF.

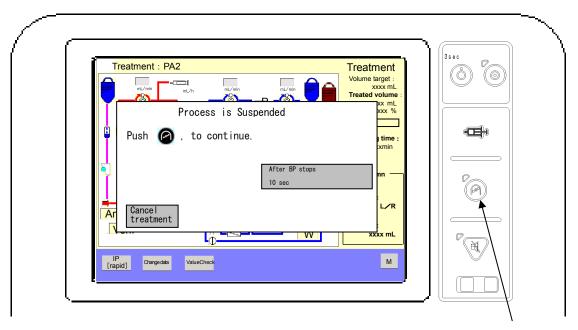


Figure 6.34 Process is Suspended Screen

**BLOOD PUMP Button** 

# 6.2.3.6 Volume target completes

When the treated plasma volume reaches the pre-set volume target, the music(by pre-set) tells the completion of the treatment and the "Volume Target Completes" screen appears on the LCD. appears.)

In case any further continuation of the treatment is desired, increase the volume target by changing data, and touch the Continue Treatment key to resume.

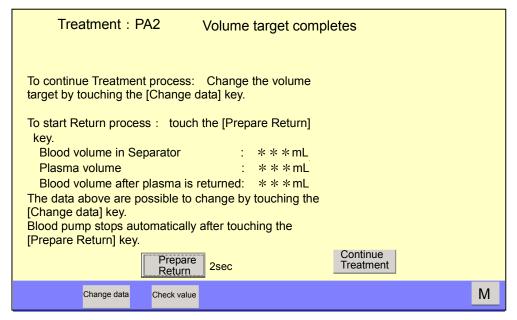


Figure 6.35 Volume Target Completes Screen

## 6.2.4 Return

1. Touch the Prepare Return key on the "Volume target completes" screen.

The Preparation of "Return" screen will appear on the LCD.

The Blood Pump stops.

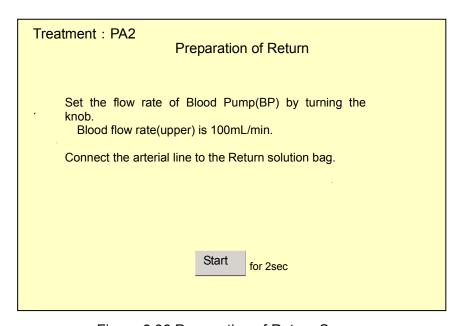


Figure 6.36 Preparation of Return Screen

- 2. Clamp the cannula and the arterial line.
- 3. Aseptically disconnect the arterial line from the cannula and connect a needle to the end of the arterial line.
- 4. Aseptically connect the arterial line to the solution bag.
- 5. Remove the infusion line from the Fluid Detector 1 (FD1) and install the arterial line instead.

6. Touch the Start key on the Preparation of "Return" screen.

The "Return" screen will appear on the LCD.

Maximum rate of Blood Pump (BP) is 100mL/min.

Return blood and plasma to the patient.

7. When the returned volume reaches the preset value, the Blood Pump stops automatically.

The "Return Completes" screen will appear on the LCD.

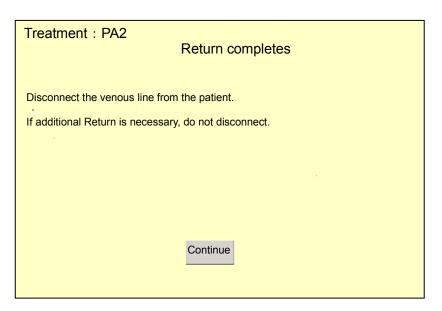


Figure 6.37 Return Completes Screen

- 8. Clamp the cannula on the venous line.
- 9. Aseptically remove the cannula from the return side of the patient.
- 10. Touch the Continue key on the "Return Completes" screen. The "Procedure" screen will appear on the LCD.

In case an additional blood return process is desired, touch the Re-Return key on the "Procedure" screen without above 8 and 9 operations.

The "Preparation of Re-Return" screen appears. Set a Re-Return volume (for "blood" side only) through the Changing data key, then touch the Start key to resume.

The Re-Return key appears in yellow color in the "Procedure" screen after the completion of Return process.



Re-Return process is applicable only to the blood side and no more plasma side is returned in Re-Return process.

# 6.2.5 Completion of the Operation

# 6.2.5.1 Disconnecting the tubing

- 1. Touch the Detach tubing key on the "Procedure" screen for 2 sec. and more, then, the confirmation window appears. Touch the YES key on the window for 2 sec. and more, then the Treatment is finished screen appears.
- 2. Disconnect the line from the solution bags.
- 3. Unclamp the roller clamp and the small clamp to open the infusion line to the atmosphere.
- 4. Put the end of the venous and waste line to the waste container.
- 5. Touch the Open valve key on "The Treatment is finished" screen.
- 6. Remove the tubing, Transducer Protective Filters, Plasma Separator, Adsorption Columns, Syringe and Solution bags.

# 6.2.6 Completion

1. Touch the Confirm key on "The Treatment is finished" screen.

The "Initial" screen will appear on the LCD.

- 2. Press the "POWER OFF" button.
- 3. Disposables (i.e., tubing, plasma separator, syringe, etc.) are to be discarded according to the local laws and regulations.
- 4. Disconnect the Mains Plug from the outlet.
- Clean or disinfect the machine according to the routine maintenance procedure described in the chapter 9.

# 7. ALARMS OF THE MA-03

# 7.1 Alarm Status

# **⚠** WARNING

Operate the MA-03 under the instructions of the physician while carefully monitoring the patient's condition.

When the alarm related to the treatment occurs, the physician should take appropriate measures.

1. There are three kinds of alarms by type of reset.

Automatic reset: When the cause of the alarm is removed, the buzzer stops and the alarm system recovers to the normal state automatically. (The term "Auto" is mentioned on the Alarm list.)

Key reset : When the cause of the alarm is removed, touch the Continue key to

recover. (The term "Key" is mentioned on the Alarm list.)

Power on/off reset: By turning off and on the machine, the MA-03 will return to normal state. (The term "Power" is mentioned on the Alarm list.)

- 2. There are four kinds of alarms by type of operation.
  - 1) The alarm related to the blood line (The term "Blood" is mentioned on the Alarm list.)

When the alarm related to the blood line (line in which blood flows) occurs, or abnormalities of the machine are detected, this machine performs the following operation.

- a. Buzzer sounds and mute switch lamp flashes.
- b. The red indication lamp lights, and the alarm screen is displayed on the LCD.
- c. The Blood Pump (BP), Plasma Pump (PP), and Replacement Fluid Pump (RP) stop.
- d. Venous valve (V12) closes.
- 2) The alarm related to the plasma line (The term "Plasma" is mentioned on the Alarm list.)

When the alarm related to the plasma line occurs, this machine performs the following operation.

- a. Buzzer sounds and mute switch lamp flashes.
- b. The red indication lamp lights, and the alarm screen is displayed on the LCD.
- c. The Plasma Pump (PP), and Replacement Fluid Pump (RP) stop.
- 3) The alarm related to the replacement fluid line (The term "Replace" is mentioned on the Alarm list.)

When the alarm related to the replacement fluid line occurs, this machine performs the following operation.

#### 7. ALARMS

- a. Buzzer sounds and mute switch lamp flashes.
- b. The red indication lamp lights, and the alarm screen is displayed on the LCD.
- c. The Replacement Fluid Pump (RP) stops.

# 7.2 Alarm display

#### 1. Buzzer sound

When alarm occurs, buzzer sounds to attract attention. The buzzer can be temporarily turned off, when the mute switch is pressed.



Press the MUTE button, to turn off the buzzer. (The preset time for the buzzer to stop is two minutes.)

The volume of the buzzer can be changed.

## 2. Lighting of indication lamp

External lamp shows four alarm states.

## [States of external lamp]

States of indication lamp		n lamp	States of alarm
Abnormal (Red)	Complete (Yellow)	Normal (Green)	
Lighting			The computer etc. is not operating normally.
Flashing			The alarm which should be handled immideately occurs.
	Flashing		It shows the operation has completed.
		Flashing	It shows the suspension of the process or restriction of the pump.

### 3. Display on the LCD

If an alarm occurs, the alarm screen will appear on the LCD.

The following classification number is allocated to the head of alarm messages.

- Treatment- related alarms (TRxxx ------)
- Function check alarms (FCxxx ------)

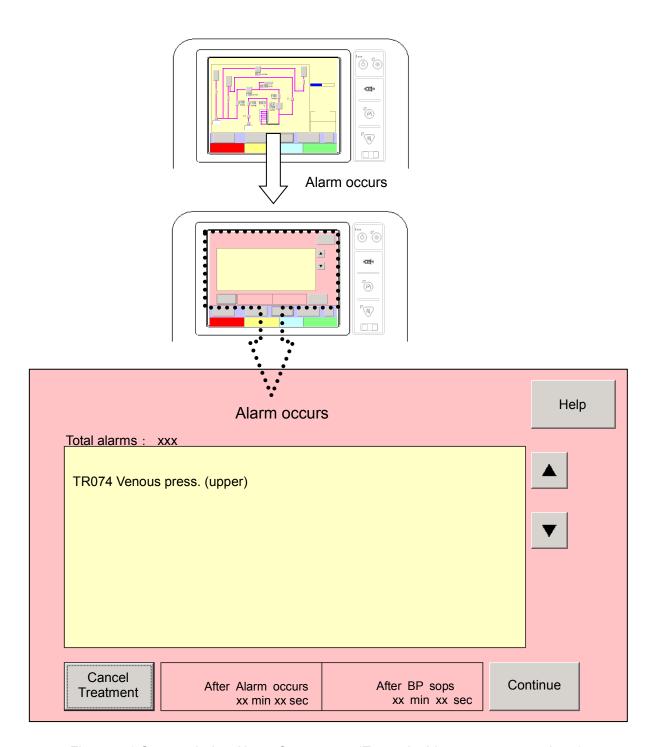


Figure 7.1 Screen during Alarm Occurrence (Example: Venous pressure alarm)



Once the "Cancel Treatment" is executed, both Treatment and Return processes are unable to continue or execute. Do not operate this key unless a premature termination of the treatment is intended.

# 7.3 Alarm point about pressure

- 1. There are three kinds of upper / lower limits of the alarm points about the pressure.
  - Automatically set alarm (only for venous pressure)
     The upper and lower points of automatically preset alarms width start monitoring the pressure after a lapse of preset time.
     Automatically preset alarm width cannot be set lower than its lower limit .
  - 2) Fixed alarm
    The presettable upper and lower points of fixed alarms work until the automatically preset alarm width is settled (automatically).
  - Critical alarm
     The upper and lower points of the critical alarms which cannot be changed .

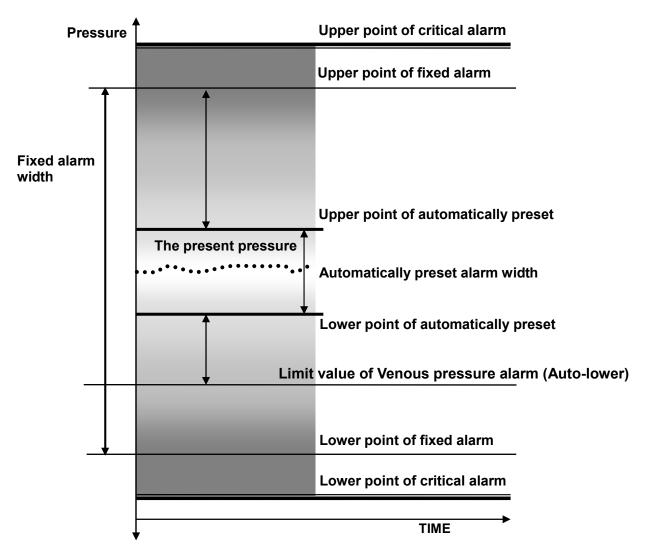


Figure 7.2 Pressure related Alarm points

# 7.4 Troubleshooting

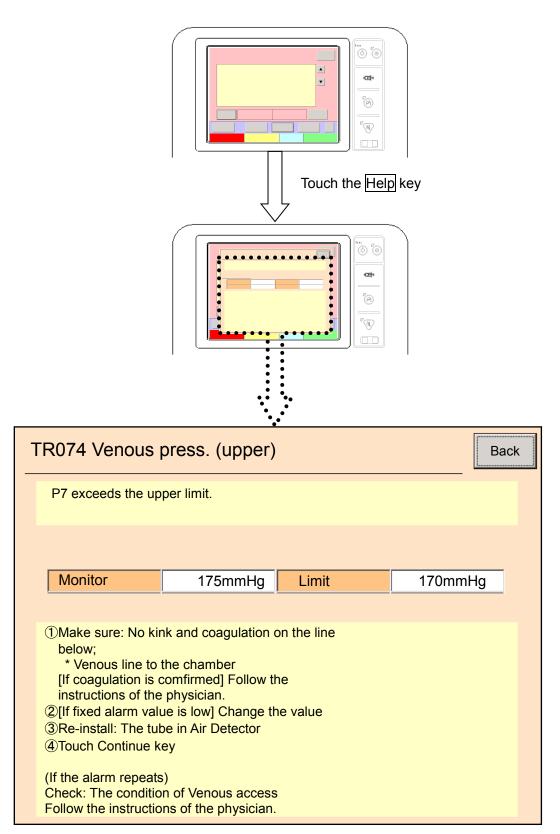


Figure 7.3 Guidance Screen (Example: Venous pressure alarm)

# **⚠** WARNING

Treatment should not be resumed until the cause of the alarm is cleared and the message disappears.

The screen is displayed by touching the Help key.

The screen consists of four frames.

- Message
- Message Description
- Display of monitored value
- Check and Measure

## Message

The message frame shows the message on the alarm screen.

# ■ Message Description

The message overview is the brief explanation of the message.

# ■ Display of monitored value

The monitored contents are displayed.

#### Check and Measure

The recommended measures are displayed. Some patient-oriented treatment that is not mentioned here may be required.



If the alarm cannot be reset after recommended procedure is taken, follow the instructions of the physician and contact the service person.

# 7.5 The recovery procedure to an alarm

## 7.5.1 Alarm related to Treatment

#### Air detector

[TR001 Bubble]

[TR002 Micro Bubble]

#### Check and Measure

- 1) Clamp the tube at outlet of the detector with clamp.
- 2) Open the door of the detector and make air bubbles in the tube flow up to Venous chamber(LD4) and close the door.
- 3) Detach the clamp from the tube.



Opening the door of the air detector is necessary to cancel alarm condition and restart treatment.

# Arterial pressure

[TR003 Arterial press.(critical lower)]

[TR004 Arterial press.(critical upper)]

[TR005 Arterial press.(lower)]

【TR006 Arterial press.(upper)】

# **Check and Measure**

- 1) Make sure: No kink of the line below: Withdrawal line to the chamber
- 2) The roller clamp on the FD1 line is open. (for Rinsing)
- 3) Open: Pressure port P1

[If P1 gets around 0mmHg] Touch Continue key.

## Blood/Saline Detector

[TR009 Detection of blood]

Check and Measure

[If blood is not running]

1) Clean: The tube and sensor

### Blood flow rate

【TR010 Low flow rate(BP)】

## **Check and Measure**

- 1) [If the upper limit of Venous pressure alarm is low] Raise: the set value
- 2) Make sure: No kink of the tube of the line below; Arterial / Venous line
- 3) Make sure: No coagulation in the line below; Arterial access to Arterial chamber
- 4) [If BP flow rate is too low] Raise: the rate by turning the knob.

## **Blood Inlet Pressure**

[TR011 Blood inlet press.(critical lower)]
[TR012 Blood inlet press.(critical upper)]

#### Check and Measure

- 1) Make sure: No kink of the tube below; Chamber to Venous chamber(P7)
- 2) Make sure: No kink and pinch of the tube below; Inlet/outlet of Blood Warmer
- 3) Open: Pressure port P2 [If P2 gets around 0mmHg] Touch Continue key.

## **Blood Leak Detector**

【TR017 Blood leak】

**Check and Measure** 

1) Make sure: There is no leak or hemolysis on the tube below; [If not confirmed] Clean the sensor and the tube.



If confirmed the blood leak, follow the instructions of the physician.

# **A**CAUTION

Avoid direct sunlight for the placement of the machine because exposure to the front panel of the machine by direct sunlight may cause an alarm of Blood Leak Detector.

# Pump Cover

[TR018 BP cover open]

[TR059 PP cover open]

[TR068 RP cover open]

**Check and Measure** 

1) Close: The cover

2) Make sure: No pinch below; Inlet / outlet of BP, Around the rotor

# Column Differential pressure

[TR020 Column(L) differential press.(upper)]

【TR021 Column(L) differential press.(lower)】

【TR022 Column(R) differential press.(upper)】

【TR023 Column(R) differential press.(lower)】

#### Check and Measure

- 1) Make sure: No kink and coagulation of tube
- 2) Make sure: No wet and leak of filter

[If confirmed] Attach a new filter adjust fluid, Level in the chamber.

3) Check: Connection of tube



If coagulation is confirmed, follow the instructions of the physician.

## Fluid detector

【TR026 Fluid empty(FD1)】

【TR027 Fluid empty (FD2)】

【TR028 Fluid empty (FD3)】

## Check and Measure

- 1) [If the solution bag is empty] Attach a new bag.
- 2) [If the solution bag is not empty]

Remove air: Air in the tube to the solution bag

Re-install: The tube Touch Continue key.

### **Blood Warmer**

[TR029 Warmer bag uninstalled]

#### Check and Measure

1) Attach: Warmer bag to Blood Warmer

## **Level Detector**

【TR030 Low level(LD1)】

[TR031 Low level(LD2)]

[TR032 Low level(LD3)]

[TR033 Low level(LD4)]

#### Check and Measure

1) [If the fluid level in the chamber is low]

Raise: Fluid level, Make sure: There is no kink or leak on the tube

2) [If the level is adequate]

Remove air: Move air to the upper part of the chamber.

Reattach: The chamber to the detector



If the Low level (LD3) alarm occur during rinsing, V1 can open by V1 key that is displayed on the alarm guidance screen.

# Conductivity Detector

#### [TR034 Conductivity error 1(Regeneration solution)]

#### Check and Measure

1) Check: Status of attachment below

Kink of the tube from Regeneration solution bag to Conductivity Detector

The tube on V1 and 2

[When Re-install the tube to the valve] Touch Re-Install tubing key

2) Check: Status of the connection and clamp below;

FD3 line to Regeneration solution bag

The clamp on the right of the V11 line is open.

3) Re-install: Conductivity sensor

[If the sensor is empty] Fill the line from the filter for Columns to the sensor with saline.

#### [TR035 Conductivity error 2(Rinsing solution)]

### **Check and Measure**

1) Check: Connection below;

FD2 line to Rinsing solution bag

#### 【TR036 Priming solution error】

#### Check and Measure

1) Check: Connection below;

FD2 line to Priming solution bag

### [TR037 Regeneration solution error]

#### Check and Measure

1) Check: Connection below;

FD3 line to Regeneration solution bag

2) Check: Install of the tubing below;

V1 to V10 respectively

3) Re-install: Conductivity Detector(CD)

[TR038 Abnormal conductivity]

[TR039 Serious abnormality of conductivity]

**Check and Measure** 

1) Check: Connection below; Replacement solution bag to the FD2 line

- 2) Make sure: No coagulation in Waste line and the conductivity sensor in the detector [If confirmed] Rinse it out of the waste line
- 3) Check: Installing of the tubing below V1 to V10 respectively

### Plasma Inlet Pressure

【TR040 Plasma inlet press.(critical lower)】

[TR041 Plasma inlet press.(critical upper)]

Check and Measure

1) Open: Pressure port P4 [If P4 gets around 0mmHg] Touch Continue key

## Plasma Outlet Pressure

【TR046 Plasma outlet press.(critical lower)】

[TR047 Plasma outlet press.(critical upper)]

Check and Measure

1) Open: Pressure port P6

[If P6 gets around 0mmHg] Touch Continue key.

### Plasma Pressure

【TR052 Plasma press.(critical lower)】

[TR053 Plasma press.(critical upper)]

Check and Measure

- 1) Make sure: No clogging and coagulation in Separator
- 2) Open: Pressure port P3

[If P3 gets around 0mmHg] Touch Continue



If coagulation is confirmed, follow the instructions of the physician.

## **Blood Warmer Cover**

[TR058 Blood Warmer cover open]

### Check and Measure

1) Check: The cover is ajar.
[If confirmed] Close the cover firmly

2) [If the pressure in the bag is high]

Open Air Detector to release the pressure.

3) Make sure: No pinch below; Inlet/outlet of Blood Warmer

# Separator Differential Pressure

[TR060 Separator differential press.(upper)]

[TR061 Separator differential press.(lower)]

#### Check and Measure

- 1) Make sure: No kink and coagulation of the line below; Chamber to Venous chamber(P7)
- 2) Make sure: No wet and leak below; Air filter of P6(Plasma outlet pressure port) [If confirmed] Attach a new filter and adjust fluid level in the chamber(P6).
- 3) Make sure: No kink and pinch below; Inlet/outlet of Blood Warmer



If coagulation is confirmed, as clogging may occur, follow the instructions of the physician.

# Replacement Fluid Pressure

[TR062 Replacement fluid press.(critical lower)]

[TR063 Replacement fluid press.(critical upper)]

### Check and Measure

- 1) Make sure: No kink of the line
- 2) Open: Pressure port P5

[If P5 gets around 0mmHg] Touch Continue

## **TMP**

[TR069 TMP(upper)]
[TR070 TMP(lower)]

#### Check and Measure

- 1) Make sure: No clogging below; Separator
- 2) Make sure: No coagulation in the tube below;

Chamber to Venous chamber(P7)

- 3) Make sure: No wet and leak below; Air filter of P3(Plasma pressure port) [If confirmed] Attach a new filter and adjust fluid level in the chamber.
- 4) Make sure: No kink of the line below; Chamber to Venous chamber(P7)
- 5) Make sure: No kink and pinch below; Inlet/outlet of Blood Warmer



If coagulation or possibility of clogging is confirmed, follow the instructions of the physician.

### Venous Pressure

【TR071 Venous press.(critical lower)】

[TR072 Venous press.(critical upper)]

## Check and Measure

- 1) Make sure: No kink on the line below; Venous line to Chamber
- 2) Re-install: The tube in Air Detector
- 3) Open: Pressure port P7

[If P7 gets around 0mmHg] Touch Continue key.

【TR073 Venous press.(lower)】

【TR075 Venous press.(Auto-lower)】 Check and Measure

- 1) Check: Venous access
- 2) Check: Connections below; Column outlet, Separator outlet, Blood Warmer outlet/inlet, Outlet/inlet of the filter for
- 3) Make sure: No leak in the line below; V9.10 to V12, Air Detector to Venous line



If the condition is not proper, follow the instructions of the physician.

[TR074 Venous press.(upper)]

【TR076 Venous press.(Auto-upper)】

Check and Measure

- 1) Make sure: No kink and coagulation on the tube below; Venous line to Chamber
- 2) [If fixed alarm value is low] Change the value
- 3) Re-install: The tube in the Air Detector



If coagulation or possibility of clogging is confirmed, follow the instructions of the physician.

### **Tube detector**

【TR078 No tube in the BLD】 【TR079 No tube in the AD】

**Check and Measure** 

1) Re-install: The tube in Air Detector or BLD

# Warmer bag leak detector

[TR080 Warmer bag leak]

Check and Measure

1) Check: Fluid leak from warmer bag.

[If not confirmed] Clean the sensor equipped to the bottom of Blood Warmer.



If confirmed the leakage, follow the instructions of the physician.

# 7.6 Manual Blood Return

If the MA-03 cannot be operated normally during the treatment because of power failure, machine failure, or other causes, the RETURN process can be accomplished manually by using the manual pump handle.

# **MARNING**

This measure should be performed under the instructions of the physician while carefully monitoring the patient's condition.

All alarms are inoperable, including the air detector.

Visually inspect the venous line, and make sure bubbles are not infused into the patient.

The venous valve (V12) is equipped in the air detector (AD). Please open the door of the air detector and be sure to remove the tube from the air detector.

# **⚠** CAUTION

In order to return the blood manually, the treatment must be canceled.

Only blood in the arterial and venous lines is returned manually.

The manual blood return procedure is shown below:

- 1. Press the "POWER OFF" button. (The power failure buzzer stops.)
- 2. Clamp the cannula tube and remove the cannula from the withdrawal side of the patient .
  - Connect the arterial line to the return solution bag.
- 3. Remove the tube from the Air detector (AD).
- 4. Open the Blood Pump cover.
- 5. Attach the manual pump handle.
- 6. Slowly turn the Blood Pump handle clockwise.
- 7. When the blood return is completed, clamp the cannula tube and remove the cannula from the return side of the patient.

# 7.7 Alarm list

# 7.7.1 Alarm related to Treatment (TRxxx)

TR No.	Alarm name	Re-start method	Alarm group	Note
TR001	Bubble	Key	Blood	Bubble was detected by Air Detector.
TR002	Micro bubble	Key	Blood	Micro bubble was detected by Air Detector.
TR003	Arterial press. (critical lower)	Key	Blood	P1 exceeds the critical lower limit.
TR004	Arterial press.(critical upper)	Key	Blood	P1 exceeds the critical upper limit.
TR005	Arterial press. (lower)	Key	Blood	P1 exceeds the lower limit.
TR006	Arterial press. (upper)	Key	Blood	P1 exceeds the upper limit.
TR009	Detection of blood	Key	Blood	Blood was detected by the Blood detector.
TR010	Low flow rate (BP)	Key	Blood	Flow rate increases too slowly.
TR011	Blood inlet press. (critical lower)	Key	Blood	P2 exceeds the critical lower limit.
TR012	Blood inlet press. (critical upper)	Key	Blood	P2 exceeds the critical upper limit.
TR017	Blood leak	Key	Blood	Blood leak is detected.
TR018	BP cover open	Auto	Blood	The BP cover is open.
TR020	Column(L) differential press.(upper)	Key	Plasma	Column(L) differential pressure exceeds the upper limit.
TR021	Column(L) differential press.(lower)	Key	Plasma	Column(L) differential pressure exceeds the lower limit.
TR022	Column(R) differential press.(upper)	Key	Plasma	Column(R) differential pressure exceeds the upper limit.
TR023	Column(R) differential press. (lower)	Key	Plasma	Column(R) differential pressure exceeds the lower limit.
TR026	Fluid empty(FD 1)	Key	Blood	Bag is empty.
TR027	Fluid empty(FD 2)	Key	Replace.	Bag is empty.
TR028	Fluid empty(FD 3)	Key	Replace.	Bag is empty.
TR029	Warmer bag uninstalled	Key	Blood	Blood warm bag is not installed.
TR030	Low Level(LD 1)	Key	Blood	Fluid level of blood inlet chamber is low.
TR031	Low level (LD 2)	Key	Plasma	Fluid level of plasma inlet chamber is low.

TR No.	Alarm name	Re-start method	Alarm group	Note
TR033	Low level(LD 4)	Key	Blood	Fluid level of venous chamber is low.
TR034	Conductivity error 1 (Regeneration solution)	Key	Blood	The conductivity is low.
TR035	Conductivity error 2(Rinsing solution)	Key	Blood	Conductivity is high.
TR036	Priming solution error	Key	Blood	Conductivity is high.
TR037	Regeneration solution error	Key	Blood	Abnormal conductivity of Regene. solution (during Regene. step).
TR038	Abnormal conductivity	Key	Blood	Abnormal conductivity of Replacement solution (after Replacement step).
TR039	Serious abnormality of conductivity	Key	Blood	The abnormalities may remain unsolved.
TR040	Plasma inlet press. (critical lower)	Key	Plasma	P4 exceeds the critical lower limit.
TR041	Plasma inlet press. (Critical upper)	Key	Plasma	P4 exceeds the critical upper limit.
TR046	Plasma outlet press. (critical lower)	Key	Plasma	P6 exceeds the critical lower limit.
TR047	Plasma outlet press. (critical upper)	Key	Plasma	P6 exceeds the critical upper limit.
TR052	Plasma press. (critical lower)	Key	Plasma	P3 exceeds the critical lower limit.
TR053	Plasma press. (critical upper)	Key	Plasma	P3 exceeds the critical upper limit.
		1.7		
TR058	Blood warmer cover open	Key	Blood	The cover is ajar.
TR059	PP cover open	Auto	Plasma	The PP cover is open.
TR060	Separator differential press. (upper)	Key	Blood	Separator differential press. exceeds the upper limit.
TR061	Separator differential press. (lower)	Key	Blood	Separator differential press. exceeds the lower limit.
TR062	Replace. fluid press. (critical lower)	Key	Replace.	P5 exceeds the critical lower limit.
TR063	Replace. fluid press. (critical upper)	Key	Replace.	P5 exceeds the critical upper limit.
TR068	RP cover open	Auto	Replace.	The RP cover is open.
TR069	TMP (upper)	Key	Plasma	TMP exceeds the upper limit.
TR070	TMP (lower)	Key	Plasma	TMP exceeds the lower limit.

TR No.	Alarm name	Re-start method	Alarm group	Note
TR071	Venous press.(critical lower)	Key	Blood	P7 exceeds the critical lower limit.
TR072	Venous press.(critical upper)	Key	Blood	P7 exceeds the critical upper limit.
TR073	Venous press. (lower)	Key	Blood	P7 exceeds the lower limit.
TR074	Venous press.(upper)	Key	Blood	P7 exceeds the upper limit.
TR075	Venous press. (Auto-lower)	Key	Blood	P7 exceeds the lower limit.
TR076	Venous press. (Auto-upper)	Key	Blood	P7 exceeds the upper limit.
TR078	No tube in BLD	Auto	Blood	The tube is not detected.
TR079	No tube in AD	Auto	Blood	The tube is not detected.
TR080	Warmer bag leak	Key	Blood	The blood warmer leaks.

# 7.7.2 Function check alarm (FCxxx)

FC	Alarm name	Re-start	Alarm	Note
No.		method	group	
FC001	Add. error exception, load (CTR)	Power	Blood	CPU failure (Control)
FC002	Add. error exception, store(CTR)	Power	Blood	CPU failure (Control)
FC003	Bus error exception, instruction (CTR)	Power	Blood	CPU failure (Control)
FC004	Bus error exception, data (CTR)	Power	Blood	CPU failure (Control)
FC005	System call exception(CTR)	Power	Blood	CPU failure (Control)
FC006	Break point exception (zero division) (CTR)	Power	Blood	CPU failure (Control)
FC007	Reserve instruction exception (CTR)	Power	Blood	CPU failure (Control)
FC008	Coprocessor unusable exception (CTR)	Power	Blood	CPU failure (Control)
FC009	Over flow exception (CTR)	Power	Blood	CPU failure (Control)
FC010	3PRAM command failure(CTR)	Power	Blood	CPU failure (Control)
FC011	3PRAM sum failure(CTR)	Power	Blood	CPU failure (Control)
FC012	3PRAM timeout failure(CTR)	Power	Blood	CPU failure (Control)
FC013	3PRAM ack failure(CTR)	Power	Blood	CPU failure (Control)
FC014	3PRAM key failure(CTR)	Power	Blood	CPU failure (Control)
FC015	3PRAM read failure(CTR)	Power	Blood	CPU failure (Control)
FC016	3PRAM address failure(CTR)	Power	Blood	CPU failure (Control)
FC017	TASK2 Error(CTR)	Power	Blood	CPU failure (Control)
FC018	TASK3 Error(CTR)	Power	Blood	CPU failure (Control)
FC019	TASK4 Error(CTR)	Power	Blood	CPU failure (Control)
FC020	TASK5 Error(CTR)	Power	Blood	CPU failure (Control)
FC021	TASK6 Error(CTR)	Power	Blood	CPU failure (Control)

FC No.	Alarm name	Re-start method	Alarm group	Note
FC022	TASK7 Error(CTR)	Power	Blood	CPU failure (Control)
FC023	TASK8 Error(CTR)	Power	Blood	CPU failure (Control)
FC024	TASK9 Error(CTR)	Power	Blood	CPU failure (Control)
FC025	TASK10 Error(CTR)	Power	Blood	CPU failure (Control)
FC026	Time Base Error(CTR)	Power	Blood	CPU failure (Control)
FC027	Process select failure (CTR)	Power	Blood	CPU failure (Control)
FC028	Treatment mode failure(CTR)	Power	Blood	CPU failure (Control)
FC029	Discrepancy of page (CTR)	Power	Blood	CPU failure (Control)
FC030	No response of step transit (PRT)	Power	Blood	CPU failure (Protective)
FC031	Discrepancy of step transit (CTR)	Power	Blood	CPU failure (Control)
FC032	Alarm status failure (CTR)	Power	Blood	CPU failure (Control)
FC033	Discrepancy of treated volume(CTR)	Power	Blood	Control CPU detect the differential treated volume just a transit process.
FC034	Select key failure (CTR)	Power	Blood	CPU failure (Control)
F0026	Failure of the CDU toot (CTD)	Damer	Disad	CDU failure (Control)
FC036	Failure of the CPU test (CTR)	Power	Blood	CPU failure (Control) [FRAM abnormal]
FC037	FRAM write error(CTR)	Power	Blood	abnormal writing.
FC038	Failure of the RAM test (CTR)	Power	Blood	[FRAM abnormal] Test failure.
FC039	Failure of ROM test (CTR)	Power	Blood	[ROM abnormal] Test failure.
FC040	Abnormal 5V (CTR)	Power	Blood	[Machine failure] Incorrect voltage
FC041	Abnormal 12V (CTR)	Power	Blood	[Machine failure] Incorrect voltage
FC042	BP volume discrepancy(CTR)	Power	Blood	Control CPU detects discrepancy in BP treated volume.
FC043	PP volume discrepancy(CTR)	Power	Blood	Control CPU detects discrepancy in PP treated volume.
FC044	RP volume discrepancy(CTR)	Power	Blood	Control CPU detects discrepancy in RP treated volume.
FC045	BP volume discrepancy (PRT)	Power	Blood	Protective CPU detects discrepancy in BP treated volume.
FC046	PP volume discrepancy (PRT)	Power	Blood	Protective CPU detects discrepancy in PP treated volume.
FC047	RP volume discrepancy (PRT)	Power	Blood	Protective CPU detects discrepancy in RP treated volume.

FC No.	Alarm name	Re-start method	Alarm group	Note
FC048	Step transit failure(CTR)	Power	Blood	CPU failure (Control)
FC049	Step transit failure(PRT)	Power	Blood	CPU failure (Protective)
FC051	Add. error exception, load(PRT)	Power	Blood	CPU failure (Protective)
FC052	Add. error exception, store(PRT)	Power	Blood	CPU failure (Protective)
FC053	Bus error exception, instruction(PRT)	Power	Blood	CPU failure (Protective)
FC054	Bus error exception, data(PRT)	Power	Blood	CPU failure (Protective)
FC055	System call exception(PRT)	Power	Blood	CPU failure (Protective)
FC056	Break point exception (zero division) (PRT)	Power	Blood	CPU failure (Protective)
FC057	Reserve instruction exception (PRT)	Power	Blood	CPU failure (Protective)
FC058	Coprocessor unusable exception (PRT)	Power	Blood	CPU failure (Protective)
FC059	Over flow exception (PRT)	Power	Blood	CPU failure (Protective)
FC060	3PRAM command failure(PRT)	Power	Blood	CPU failure (Protective)
FC061	3PRAM sum failure(PRT)	Power	Blood	CPU failure (Protective)
FC062	PRAM timeout failure(PRT)	Power	Blood	CPU failure (Protective)
FC063	3PRAM ack failure(PRT)	Power	Blood	CPU failure (Protective)
FC064	3PRAM key failure(PRT)	Power	Blood	CPU failure (Protective)
FC065	3PRAM read failure(PRT)	Power	Blood	CPU failure (Protective)
FC066	3PRAM address failure(PRT)	Power	Blood	CPU failure (Protective)
FC067	TASK2 Error(PRT)	Power	Blood	CPU failure (Protective)
FC068	TASK3 Error(PRT)	Power	Blood	CPU failure (Protective)
FC069	TASK4 Error(PRT)	Power	Blood	CPU failure (Protective)
FC070	TASK5 Error(PRT)	Power	Blood	CPU failure (Protective)
FC071	TASK6 Error(PRT)	Power	Blood	CPU failure (Protective)
FC072	TASK7 Error(PRT)	Power	Blood	CPU failure (Protective)
FC073	TASK8 Error(PRT)	Power	Blood	CPU failure (Protective)
FC074	TASK9 Error(PRT)	Power	Blood	CPU failure (Protective)
FC075	TASK10 Error(PRT)	Power	Blood	CPU failure (Protective)
FC076	Time Base Error(PRT)	Power	Blood	CPU failure (Protective)
FC077	Process select failure (PRT)	Power	Blood	CPU failure (Protective)
FC078	Treatment mode failure (PRT)	Power	Blood	CPU failure (Protective)
FC079	Discrepancy of page (PRT)	Power	Blood	CPU failure (Protective)
FC080	No response of step transit (CTR)	Power	Blood	CPU failure (Control)
FC081	Discrepancy of step transit (PRT)	Power	Blood	CPU failure (Protective)
FC082	Alarm status failure (PRT)	Power	Blood	CPU failure (Protective)
FC083	Discrepancy of treated volume(PRT)	Power	Blood	CPU failure (Protective)

FC No.	Alarm name	Re-start method	Alarm group	Note
FC084	Select key failure (PRT)	Power	Blood	CPU failure (Protective)
FC086	Failure of CPU test (PRT)	Power	Blood	CPU failure (Protective)
FC087	FRAM write error (PRT)	Power	Blood	Abnormal write to the data memory (Protective)
FC088	Failure of RAM test (PRT)	Power	Blood	Failure of the data memory (Protective)
FC089	Failure of ROM test (PRT)	Power	Blood	Failure of the ROM (Protective)
FC090	Abnormal 5V (PRT)	Power	Blood	[Machine failure] Incorrect voltage (Protective)
FC091	Abnormal 12V (PRT)	Power	Blood	[Machine failure] Incorrect voltage (Protective)
FC101	Add. error exception, load(ITF)	Power	Blood	CPU failure (Interface)
FC102	Add. error exception, store(ITF)	Power	Blood	CPU failure (Interface)
FC103	Bus error exception, instruction(ITF)	Power	Blood	CPU failure (Interface)
FC104	Bus error exception, data(ITF)	Power	Blood	CPU failure (Interface)
FC105	System call exception(ITF)	Power	Blood	CPU failure (Interface)
FC106	Break point exception (zero division) (ITF)	Power	Blood	CPU failure (Interface)
FC107	Reserve instruction exception (ITF)	Power	Blood	CPU failure (Interface)
FC108	Coprocessor unusable exception (ITF)	Power	Blood	CPU failure (Interface)
FC109	Over flow exception (ITF)	Power	Blood	CPU failure (Interface)
FC110	3PRAM command failure(ITF)	Power	Blood	CPU failure (Interface)
FC111	3PRAM sum failure(ITF)	Power	Blood	CPU failure (Interface)
FC112	PRAM timeout failure(ITF)	Power	Blood	CPU failure (Interface)
FC113	3PRAM ack failure(ITF)	Power	Blood	CPU failure (Interface)
FC114	3PRAM key failure(ITF)	Power	Blood	CPU failure (Interface)
FC115	3PRAM read failure(ITF)	Power	Blood	CPU failure (Interface)
FC116	3PRAM address failure(ITF)	Power	Blood	CPU failure (Interface)
FC117	TASK2 Error(ITF)	Power	Blood	CPU failure (Interface)
FC118	TASK3 Error(ITF)	Power	Blood	CPU failure (Interface)
FC119	TASK4 Error(ITF)	Power	Blood	CPU failure (Interface)
FC120	TASK5 Error(ITF)	Power	Blood	CPU failure (Interface)
FC121	TASK6 Error(ITF)	Power	Blood	CPU failure (Interface)
FC122	TASK7 Error(ITF)	Power	Blood	CPU failure (Interface)
FC123	TASK8 Error(ITF)	Power	Blood	CPU failure (Interface)
FC124	TASK9 Error(ITF)	Power	Blood	CPU failure (Interface)

FC No.	Alarm name	Re-start method	Alarm group	Note
FC125	TASK10 Error(ITF)	Power	Blood	CPU failure (Interface)
FC126	Time Base Error(ITF)	Power	Blood	CPU failure (Interface)
FC136	Failure of CPU test (ITF)	Power	Blood	CPU failure (Interface)
FC137	FRAM write error(ITF)	Power	Blood	Abnormal write to the data memory (Interface)
FC138	Failure of RAM test (ITF)	Power	Blood	Failure of the data memory (Interface)
FC139	Failure of ROM test (ITF)	Power	Blood	Failure of the ROM (Interface)
FC151	Failure of 3PRAM test	Power	Blood	3PRAM failure
FC152	Database [Adjustment data 1] check sum abnormal	Power	Blood	Database of adjustment data 1 is abnormal (Check sum)
FC153	Database [Adjustment data 1] version unmatched	Power	Blood	Database of adjustment data 1 is abnormal (Version)
FC154	Database [Adjustment data 2] check sum abnormal	Power	Blood	Database of adjustment data 2 is abnormal (Check sum)
FC155	Database [Adjustment data 2] version unmatched	Power	Blood	Database of adjustment data 2 is abnormal (Version)
FC156	Database [Adjustment data 3] check sum abnormal	Power	Blood	Database of adjustment data 3 is abnormal (Check sum)
FC157	Database [Adjustment data 3] version unmatched	Power	Blood	Database of adjustment data 3 is abnormal (Version)
FC158	Database [Working data 1] check sum abnormal	Power	Blood	Database of working data 1 is abnormal (Check sum)
FC159	Database [Working data 1] version unmatched	Power	Blood	Database of working data 21is abnormal (Version)
FC160	Database [Working data 2] check sum abnormal	Power	Blood	Database of working data 2 is abnormal (Check sum)
FC161	Database [Working data 2] version unmatched	Power	Blood	Database of working data 2 is abnormal (Version)
FC162	Database [Setting data 1] discrepancy	Power	Blood	Database of setting data 1 is abnormal (Discrepancy)
FC163	Database [Setting data 1] check sum abnormal	Power	Blood	Database of setting data 1 is abnormal (Check sum)
FC164	Database [Setting data 1] version unmatched	Power	Blood	Database of setting data 1 is abnormal (Version)
FC165	Database [Setting data 2] check sum abnormal	Power	Blood	Database of setting data 2 is abnormal (Check sum)

FC No.	Alarm name	Re-start method	Alarm group	Note
FC166	Database [Setting data 2] version unmatched	Power	Blood	Database of setting data 2 is abnormal (Version)
FC167	Database [Treatment data 1] check sum abnormal	Power	Blood	Database of treatment data 1 is abnormal (Check sum)
FC168	Database [Treatment data 1] version unmatched	Power	Blood	Database of treatment data 1 is abnormal (Version)
FC169	Database [Treatment data 2] check sum abnormal	Power	Blood	Database of treatment data 2 is abnormal (Check sum)
FC170	Database [Treatment data 2] version unmatched	Power	Blood	Database of treatment data 2 is abnormal (Version)
FC171	Abnormal check sum of Database[Adjust.data4]	Power	Blood	[Database failure]
FC172	Mismatched Ver. of Databas [Adjust. data4]	Power	Blood	[Database failure]
FC196	Touch key failure	Power	Blood	Touch key turns on more than regulated time.
FC197	Pump power switch failure	Power	Blood	Pump power SW turns on more than regulated time.
FC198	Mute switch failure	Power	Blood	Buzzer mute SW turns on more than regulated time.
FC201	Air detector (Test signal)	Key	Blood	[Sensor abnormality] Abnormal signal was detected by Air Detector in continuous test.
FC202	Air detector (Bubble)	Key	Blood	[Sensor abnormality] Abnormality was detected by Air Detector in continuous test.
FC203	Air detector (Micro Bubble)	Key	Blood	[Sensor abnormality] Abnormality was detected by Air Detector in continuous test.
FC204	Failure of Air detector(AD) test	Key	_	Self test: Abnormality of air detector was detected.
				Colf toots Abroamos life of
FC206	Failure of Conductivity Detector test	Key	_	Self test: Abnormality of conductivity detector was detected.
FC211	Failure of Level Detector(LD 1) test	Key	_	Self test: LD1 detects high level
FC212	Failure of Level Detector(LD 3) test	Key	_	Self test: LD3 detects high level
FC213	Failure of Level Detector(LD 4) test	Key	_	Self test: LD4 detects high level
FC214	Failure of Level Detector(LD 2) test	Key		Self test: LD2 detects high level
FC216	Failure of Fluid detector(FD 1) test	Key	_	Self test: FD1 detects fluid
FC217	Failure of Fluid detector(FD 2) test	Key	_	Self test: FD2 detects fluid

FC No.	Alarm name	Re-start method	Alarm group	Note
FC218	Failure of Fluid detector(FD 3) test	Key	_	Self test: FD3 detects fluid
FC221	Step error 1(No detection of fluid;AD)	Key	Blood	[Step error] Fluid does not reach AD.
FC222	Step error 2(No detection of fluid level; LD1)	Key	Blood	[Step error] Fluid does not reach LD1.
FC223	Step error 3(Fluid level remains high;LD1)	Key	Blood	[Step error] Fluid level does not fall.
FC224	Step error 4(Fluid level remains low;LD2)	Key	Blood	[Step error] Fluid level does not rise.
FC225	Step error 5(No detection of fluid;LD3)	Key	Blood	[Step error] Fluid level does not rise.
FC226	Step error 6(Fluid level remains low;LD4)	Key	Blood	[Step error] Fluid level does not rise.
FC227	Step error 7(Fluid level remains high ;LD2)	Key	Blood	[Step error] Fluid level does not fall.
FC228	Step error 8(Fluid level remains high;LD3)	Key	Blood	[Step error] Fluid level does not fall.
FC229	Step error 9(Fluid level remains high ;LD4)	Key	Blood	[Step error] Fluid level does not fall.
FC301	Press.diff. between 2 Arterial press.sensors	Key	Blood	Abnormality of the machine
FC302	Failure of Arterial press. test (CTR)	Key	_	Abnormality of Arterial pressure sensor P1 in atmosphere
FC303	Failure of Arterial press. test (PRT)	Key	_	Abnormality of Arterial pressure sensor P8 in atmosphere
FC304	Failure of Blood inlet press. test	Key	_	Abnormality of Arterial pressure sensor P2 in atmosphere
FC305	Failure of Plasma press. test	Key	_	Abnormality of Plasma pressure sensor P3 in atmosphere
FC306	Failure of Plasma inlet press. test	Key	_	Abnormality of Plasma inlet pressure sensor P4 in atmosphere
FC307	Failure of Plasma Outlet press. test	Key	_	Abnormality of Plasma outlet pressure sensor P6 in atmosphere
FC308	Failure of Replacement Fluid press. test	Key	_	Abnormality of Plasma replacement pressure sensor P6 in atmosphere
FC309	Failure of Venous press. test failure	Key	_	Abnormality of venous pressure sensor P7 in atmosphere
FC311	Span test error of P2 or P7	Key	Blood	Pressure differs more than 10mmHg between P2 and P7.

FC No.	Alarm name	Re-start method	Alarm group	Note
FC312	Span test error of P3 or P6	Key	Blood	Pressure differs more than 10mmHg between P3 and P6.
FC313	Span test error of P4 or P5	Key	Blood	Pressure differs more than 10mmHg between P4 and P5.
FC401	Offset of Blood detector	Key	Blood	[Sensor failure] Abnormal offset of the Blood Detector
FC411	Rejected on BLD test	Key	Blood	[Sensor abnormality] Failure of the BLD test
FC412	BLD volt. (green/upper)	Key	Blood	[Sensor abnormality] Output of BLD green is abnormal.
FC413	BLD volt. (green/lower)	Key	Blood	[Sensor abnormality] Abnormal output of BLD.
FC414	BLD volt.(red/upper)	Key	Blood	[Sensor abnormality] Abnormal output of BLD.
FC415	BLD volt.(red/lower)	Key	Blood	[Sensor abnormality] Abnormal output of BLD.
FC416	BLD not clear(green)	Key	Blood	[Sensor abnormality] Low output of the BLD.
FC417	BLD not clear(red)	Key	Blood	[Sensor abnormality] Low output of the BLD.
FC422	Failure of Thermistor comparison test(zero)	Key	_	Self test: Machine failure
FC424	Failure of Heater relay test	Key	_	Self test: A heater relay does not work.
FC425	Span test error of TH1 and TH2	Key	Blood	Temperature differs more than 1 degree between TH1 and TH2.
FC426	Abnormal blood warmer temperature	Key	Blood	[Machine failure] Temperature exceeds alarm value.
FC429	Breaking of TH1 wire	Power	Blood	Self test: Machine failure
FC430	Short circuit of TH1 wire	Power	Blood	Self test: Machine failure
FC431	Breaking of TH2 wire	Power	Blood	Self test: Machine failure
FC432	Short circuit of TH2 wire	Power	Blood	Self test: Machine failure
FC501	Failure of BP test	Key	_	Self test: Abnormality in BP operation (normal rotation)

FC No.	Alarm name	Re-start method	Alarm group	Note
FC502	Failure of BP test(reverse)	Key	_	Self test: Abnormality in BP operation (reversal rotation)
FC503	Failure of BP test(stop) (CTR)	Key	_	Self test: Abnormality BP operation (stop from control)
FC504	Failure of BP test(stop) (PRT)	Key	_	Self test: Abnormality BP operation (stop from protection)
FC505	High flow rate (BP)	Key	Blood	[Pump failure] Flow rate exceeds the upper limit.
FC506	Low flow rate (BP)	Key	Blood	[Pump failure] Flow rate exceeds the lower limit.
FC507	Uncontrollable BP	Key	Blood	[Pump failure] Control on BP fails.
FC508	Overload to BP	Key	Blood	[Pump failure] BP is uncontrollable.
FC509	BP reverse rotation	Key	Blood	[Pump failure] BP rotates reversely.
FC511	Failure of PP test	Key	_	Self test: Abnormality in PP operation (normal rotation)
FC512	Failure of PP test(reverse)	Key	_	Self test: Abnormality in PP operation (reversal rotation)
FC513	Failure of PP test(stop) (CTR)	Key	_	Self test: Abnormality in PP operation (stop from control)
FC514	Failure of PP test(stop) (PRT)	Key	_	Self test: Abnormality in PP operation (stop from protection)
FC515	High flow rate (PP)	Key	Blood	[Pump failure] Flow rate exceeds the upper limit.
FC516	Low flow rate (PP)	Key	Blood	[Pump failure] Flow rate exceeds the lower limit.
FC517	Uncontrollable PP	Key	Blood	[Pump failure] Control on PP fails.
FC518	Overload to PP	Key	Blood	[Pump failure] PP is uncontrollable.
FC519	PP reverse rotation	Key	Blood	[Pump failure]
FC521	Failure of RP test	Key	_	Self test: Abnormality in RP operation (normal rotation)

FC	Alarm name	Re-start	Alarm	Note
No.		method	group	Self test: Abnormality in
FC522	Failure of RP test(reverse)	Key	_	RP operation (reversal rotation)
FC523	Failure of RP test(stop) (CTR)	Key	_	Self test: Abnormality in RP operation (stop from control)
FC524	Failure of RP test(stop) (PRT)	Key	_	Self test: Abnormality in RP operation (stop from protection)
FC525	High flow rate (RP)	Key	Blood	[Pump failure] Flow rate exceeds the upper limit.
FC526	High flow rate (RP)	Key	Blood	[Pump failure] Flow rate exceeds the upper limit.
FC527	Uncontrollable RP	Key	Blood	[Pump failure] Control on RP fails.
FC528	Overload to RP	Key	Blood	[Pump failure] RP is uncontrollable.
FC529	RP reverse rotation	Key	Blood	[Pump failure] RP rotates reversely.
FC531	Pump tube uninstalled	Key	Blood	Pump tube is not installed.
FC541	Failure of IP test	Key	_	Self test: Abnormality in IP operation
FC542	Failure of IP test(stop) (CTR)	Key	_	Self test: Abnormality in IP operation (stop by control)
FC543	Failure of IP test(stop) (PRT)	Key	_	Self test: Abnormality in IP operation (stop by protection)
FC544	High flow rate (IP)	Key	Blood	[Pump failure] Flow rate exceeds the upper limit.
FC545	Low flow rate (IP)	Key	Blood	[Pump failure] Flow rate exceeds the lower limit.
FC546	IP reverse movement	Key	Blood	[Pump failure] Infusion pump (IP) moves backward.
EC604	Egilure of \/4 toot/class\	Kovi		V4 connet be closed
FC601	Failure of V1 test(close)	Key	_	V1 cannot be closed
FC602	Failure of V1 test(open)	Key	_	V1 cannot be opened
FC603 FC604	Failure of V2 test(close)	Key	_ 	V2 cannot be closed V2 cannot be opened
FC605	Failure of V2 test(open)  Failure of V3 test(close)	Key Key	_	V3 cannot be opened
FC606	Failure of V3 test(close)	Key		
FC607	Failure of V4 test(close)	Key	_	V3 cannot be opened V4 cannot be closed
FC608	Failure of V4 test(close)	Key	_   <b>_</b>	V4 cannot be closed V4 cannot be opened
1 0000	i anule of V4 test(open)	I Ve A		v - camilot be opened

FC No.	Alarm name	Re-start method	Alarm group	Note
FC609	Failure of V5 test(close)	Key	_	V5 cannot be closed
FC610	Failure of V5 test(open)	Key	_	V5 cannot be opened
FC611	Failure of V6 test(close)	Key	_	V6 cannot be closed
FC612	Failure of V6 test(open)	Key	_	V6 cannot be opened
FC613	Failure of V7 test(close)	Key	_	V7 cannot be closed
FC614	Failure of V7 test(close) (PRT)	Key	_	V7 cannot be closed (from protection)
FC615	Failure of V7 test(open)	Key	_	V7 cannot be opened
FC616	Failure of V8 test(close)	Key	_	V8 cannot be closed
FC617	Failure of V8 test(close) (PRT)	Key	_	V8 cannot be closed (from protection)
FC618	Failure of V8 test(open)	Key	_	V8 cannot be opened
FC619	Failure of V9 test(close)	Key	_	V9 cannot be closed
FC620	Failure of V9 test(open)	Key	_	V9 cannot be opened
FC621	Failure of V10 test(close)	Key	_	V10 cannot be closed
FC622	Failure of V10 test(open)	Key	_	V10 cannot be opened
FC623	Failure of V11 test(close)	Key	_	V11 cannot be closed
FC624	Failure of V11 test(close) (PRT)	Key	_	V11 cannot be closed (from protection)
FC625	Failure of V11 test(open)	Key	_	V11 cannot be opened
FC626	Failure of V12 test(close)	Key	_	V12 cannot be closed
FC627	Failure of V12 test(close) (PRT)	Key	_	V12 cannot be closed (from protection)
FC628	Failure of V12 test(open)	Key	_	V12 cannot be opened
FC631	valve 1 error	Key	Blood	Valve 1 does not open / close.
FC632	valve 2 error	Key	Blood	Valve 2 does not open / close.
FC633	valve 3 error	Key	Blood	Valve 3 does not open / close.
FC634	valve 4 error	Key	Blood	Valve 4 does not open / close.
FC635	valve 5 error	Key	Blood	Valve 5 does not open / close.
FC636	valve 6 error	Key	Blood	Valve 6 does not open / close.
FC637	valve 7 error	Key	Blood	Valve 7 does not open / close.
FC638	valve 8 error	Key	Blood	Valve 8 does not open / close.
FC639	valve 9 error	Key	Blood	Valve 9 does not open / close.
FC640	valve 10 error	Key	Blood	Valve 10 does not open / close.
FC641	valve 11 error	Key	Blood	Valve 11 does not open / close.

FC No.	Alarm name	Re-start method	Alarm group	Note
FC642	valve 12 error	Key	Blood	Valve 12 does not open / close.
FC701	Leak error 1	Key	Blood	Rinsing (leak test): P6 does not rise. (30sec, 150mmHg)
FC702	Leak error 2	Key	Blood	Rinsing (leak test): P4 rises more than 10mmHg.
FC703	Leak error 3	Key	Blood	Rinsing (leak test): P5 rises more than 10mmHg.
FC705	Leak error 5	Key	Blood	Rinsing (leak test): P5 does not rise. (30sec, 150mmHg)
FC706	Leak error 6	Key	Blood	Rinsing (leak test): Any of P2,P3,P4,P5,P6,P7 doesn't keep the level. (The pressure falls more than 20mmHg)
FC708	Leak error 8	Key	Blood	Rinsing (leak test): P5 does not rise. (30sec, 200mmHg)
FC709	Leak error 9	Key	Blood	Rinsing (leak test): P4 rises more than 10mmHg.
FC710	Leak error 10	Key	Blood	Rinsing (leak test): P6 rises more than 10mmHg.

# 7.7.3 Information (DMxxx)

DM No.	Information Name	Re-start method	Alarm Group	Note
DM001	IP completed	Auto	Inform.	IP infusion completed
DM002	Rinse completed	Auto	Inform.	Rinsing completed
DM003	Priming completed	Auto	Inform.	Priming completed
DM004	Treatment completed	Auto	Inform.	Volume target completed
DM005	Return completed	Auto	Inform.	Return completed
DM006	No syringe	Auto	Inform.	The syringe isn't set.
DM007	IP setting value is 0	Auto	Inform.	IP flow rate isn't set.
DM008	PU temperature rise	Auto	Inform.	Internal of PU temperature rose

#### 7. ALARMS

## 8. DATA RECORD FUNCTION OF THE MA-03

The MA-03 has three kinds of data record function which are mentioned below:

- > Alarm history
- > Graph display
- > Data logging

#### 8.1 Alarm history

#### 8.1.1 Outline

The history of the alarm occurrence is recorded.

Every alarm is recorded from "Install the tubing" to "Detach the tubing".

When the "Install the tubing" process for next treatment is selected, previous data is cleared.

#### 8.1.2 The display method

1. The alarm history can be confirmed by touching the Alarm history/Graph key in the maintenance mode menu.

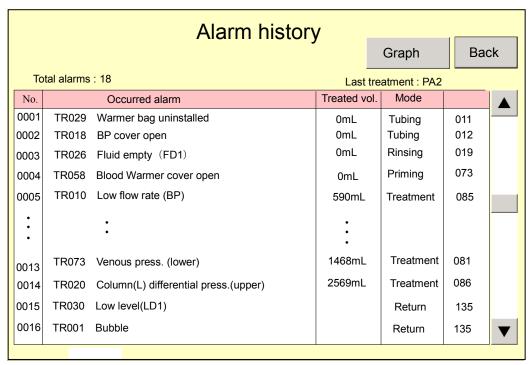


Figure 8.1 Alarm History Screen

2. One screen shows up to 16 alarm histories, and the following data is displayed on the following page. The next / previous page can be seen by touching the scroll bar on the right side of the page.

- 3. Displayed treated volume is:
  - a. Before treatment: 0mL
  - b. During treatment: Treated volume at the time of alarm occurrence
  - c. After treatment: The em dashes
- 4. Displayed process is:
  - a. During the installation of the tubing: "Tubing"
  - b. During rinsing: "Rinsing"
  - c. During priming: "Priming"
  - d. During treatment: "Treatment"
  - e. During return: "Return"
  - f. After return: "Return"

#### 8.2 Graph display

#### 8.2.1 Outline

The data of the pressure in the extra corporeal circuit is recorded and displayed by a graph.

The data is recorded from Treatment to Return.

#### 8.2.2 The display method of pressure graph

1. Displayed items differ, depending on the treatment. Here is the list of the items.

Treatment method	Displayed items				
PA2	Venous	Arterial	TMP	Separator	Plasma inlet
	press.	press.		press. loss	press.

- 2. Method to display the screen
  - a. During treatment or return process

    If the Check value key is displayed, the graph can be displayed. Touch the Check value key and display the "Check Value" screen. And touch the Graph key.
  - b. During maintenance mode (In this case, last treatment data is displayed)
    Touch the Alarm history/Graph key on the "Mode Menu" screen and display the
    "Alarm History" screen. And touch the Graph key.
- 3. The method to operate the "Graph" screen

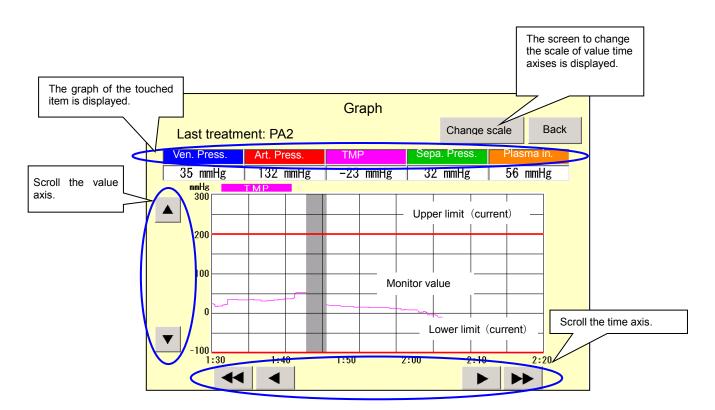


Figure 8.2 Graph Screen (of blood circuit pressure)

#### 8.3 Data logging

#### 8.3.1 Outline

The treatment data for every preset volume and alarm data for every alarm occurrence is recorded to a memory card.

It records one file for every treatment data, and the maximum amount is 150 files. The files are overwritten in the recorded order when the amount exceeds 150.

If the memory card is connected to a personal computer, the data can be read and processed with some applications, such as Microsoft Excel.

# **⚠** WARNING

Clinical data logged on the card shall not be used for other purpose than a reference of the physician in charge of the patient.

#### 8.3.2 Corresponding card

Compact flash card (Type 1)

1) Memory size 4MB 512MB

2) Format type : FAT163) Drive voltage : 3.3V

# **⚠** CAUTION

A compact flash card formatted on Windows-XP may sometimes not function properly. Format it with other OS than Windows-XP.

A commercially available preformatted CF card is recommended to use.

Insert the card to the data logging unit that is mounted at the rear of the machine.

# **⚠** CAUTION

Confirm the Card IN Lamp of the Data Logging unit is lit when a card is inserted. In case the Card IN Lamp is not lit while a card is inserted, the card may not be properly recognized. Extract the card once and reinsert it.

While the unit is accessing the card, the ACCESS Lamp on the Data Logging unit is lit. Do not remove the card while the lamp is lit, or the card may be damaged. Do not pull it out while lighting.

#### 8.3.3 The data classification and items which are recorded

#### 1. Header data

Treatment mode, condition, and status are recorded on the head of a file. Recorded data

PA2		
Date (When the tubing is installed)		
Patient No. (4-digit number)		
Machine name, Serial No., Version		
Treatment mode		
_		
Result of start-up test		
Volume target		
Treated value		
Infused volume (IP)		
_		
Start Treatment		
Return completes		
Return volume (in the Separator)		
Return volume (out of Separator)		
Return volume (after plasma in returned)		

#### 2. Treatment data

The treatment data for every volume that was preset by every facility are recorded.

#### Recorded data

recorded data			
Item	PA2		
Time	Clock time and relative time based on the start of installing the tubing.		
Treated volume	Plasma treated volume		
Pump flow rate	Blood pump(BP) flow rate Plasma pump(PP) flow rate, Infusion pump(IP) rate		
Pressure value	Arterial press. Venous press. Blood inlet press. Separator differential press. TMP Column differential press. (left)/(right)		
Other	Blood leak ratio, Temperature Conductivity, BLD voltage		

#### 8. DATA RECORD FUNCTION

#### 3. Alarm history data

Alarm data is recorded every time alarm occurs.

#### Recorded data

PA2
Sequential numbers
Clock time and relative time based on the start of installing the tubing.
The contents of the alarm.
Treated volume.
The process at the time of alarm occurrence.
The step at the time of alarm occurrence
Alarm point (Only for pressure alarm)
The value by which the alarm is generated (Only for pressure alarm)

#### 4. Time at processes switched

Start of Installing the tubing, Rinsing start, Priming completion, Treatment start, Treatment target reached time, Return start, Re-priming start, Re-return start

Recorded data: Clock time and relative time based on the start of installing the tubing.

#### 5. Operation status data

The data shows the condition of operation.

The data is recorded at Treatment start, Return completion, and every preset volume (same as the treatment).

#### Recorded data

PA2		
Clock time and relative time based on the start of installing the tubing		
Treated volume		
Volume target		
Return volume (inside and outside of the separator, after plasma return)		
Re-returning volume		
Arterial pressure alarm (upper/lower)		
Venous pressure alarm (upper/lower)		
Venous pressure (Auto-upper/lower)		
Limit value of Venous pressure alarm (Auto-lower)		
TMP alarm (upper)		
Column differential pressure alarm (upper)		
Temperature target of Blood Warmer		
FD 1 Valid / Invalid		
BLD second calibration Before / After		

#### 6. Information of Rinsing/Priming

PA2	
Rinsing/Priming	Separate/Package
Rinsing volume (B	lood paths of Separator)
Rinsing Volume (C	Columns)
Priming volume (B	lood paths of Separator)
Priming volume (C	columns)

#### 8.3.4 The method of operation

- Selection of valid or invalid
   To use the data logging, select the "valid " on the "Facility Data" screen in the maintenance mode. (Selection of Data Logging> Facility data Common Parameter for Facility ).
- 2. Selection of interval to log data

  Select the interval to log data on the "Facility Data" screen in the maintenance mode.

  (Interval to logging data > Facility data Common Parameter for Facility).
- 3. Before using the data logging
  After touching the Confirm key on the "Treatment Mode Selection 3" screen, Selection of "Data Logging" screen is displayed.

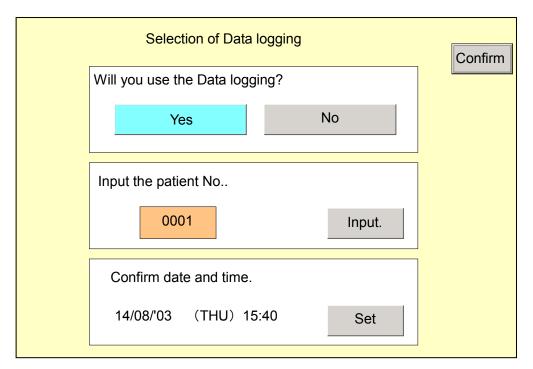


Figure 8.3 Selection of Data Logging Screen

- a. To use Data logging: Select Yes key.
- b. No to use Data logging: Select No key.
- c. Input the patient No. (4-figure number) and touch the Confirm key.



Time is necessary to manage the date file on the card. If the time displayed on the LCD is not correct, touch the Set key and set the time.

#### 8. DATA RECORD FUNCTION

#### 4. After using the data logging

To use the Data logging, touch the Confirm key on the "Treatment is Finished" screen after the treatment is finished.

The "Saving the Data" screen is displayed. The data is recorded on the card from the machine.

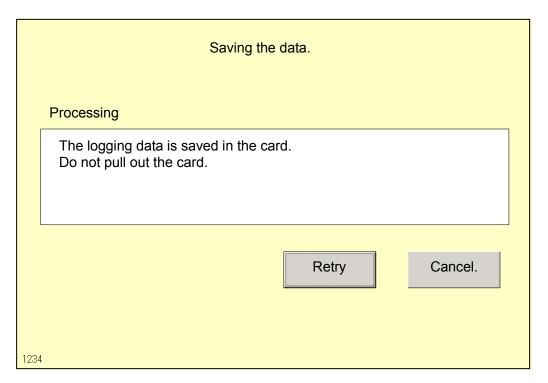


Figure 8.4 Saving the Data Screen

After data logging to the card completes normally, this screen closes automatically.

If the card is not inserted, the message "Please insert the card" appears, and Cancel key is displayed. To cancel the data logging, touch the Cancel key.

If abnormality occurs during the data logging, the Retry key is displayed. To re-save, touch the Retry key.

#### 8.3.5 File management

File in the card can be managed in the maintenance mode.

Touch the Logging data management key and Management of the "Logging Data" screen is displayed. (Management of the Logging data > Facility data - Common)

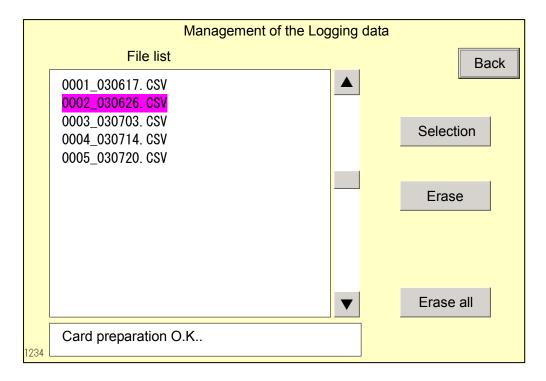


Figure 8.5 Management of the Logging Data Screen

The files in the card are read and file names are displayed on the screen. Select the file name and touch the Selection key. Selected file name is displayed in aqua.

To erase the selected file, touch the Erase key.

If you touch the Erase all key, all files in the card are erased.

#### 8. DATA RECORD FUNCTION

# 9. MAINTENANCE AND INSPECTION OF THE MA-03

# **MARNING**

The operating life of the MA-03 and its optimum operating conditions depend much upon regular care, maintenance, and meticulous performance of safety-related inspections.

# **⚠** WARNING

- 1. Before you take care of the MA-03, make sure that the power plug is not connected to the AC power outlet to avoid an electric shock.
- Do not put the accessories in any solution. Prevent fluid from flowing into inside the machine.
- 3. When using the disinfectant, follow the manufacturer's instructions.
- 4. After cleaning, confirm the MA-03 is dry before the Mains plug is connected to the AC power outlet.

#### **9.1 Care**

#### 9.1.1 Cleaning the Surface



Do not use the solvent (i.e. thinner and benzine) or abrasive cleanser.

They may damage the surface of the MA-03.

Never use undiluted sodium hypochlorite concentrate solution (bleaching agent).

Use of agent containing up to 70% of alcohol is allowed.

Accessories should not be sterilized with autoclave or high-density ozone.



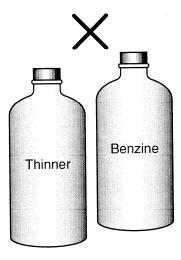
Based on the rules set by medical institutions, cleaning should be conducted with see the following description.

Clean surface with a squeezed soft cloth moistened with a diluted neutral detergent or diluted disinfectant alcohol.

Do not touch the connector assembly and never moisten it.

Care of the unit's exterior should be performed with a MOIST cloth. For surface disinfection, the cloth may be moistened with a diluted sodium hypochlorite solution (max. concentration of 0.5%).





#### 9.2 Inspection Before Use



For safe and proper use, inspecting the MA-03 before use has to be done.



At the Beginning of the Day:

Prior to daily use, the following points should be confirmed.

#### 9.2.1 Prior to Turning Power On

#### External View

- 1. No deformation due to moving.
- 2. The MA-03 should be clean.
- 3. The MA-03 should be dry.
- 4. There should be no damaged part.

#### Power Cord

- 1. No heavy object is placed on the power cord.
- 2. There should be no damage to the power cord. (No core reveals. The wire should not come down.)
- 3. The power cord should be connected to the outlet with grounding line.

#### 9.2.2 After Turning Power On

#### External View

- 1. There should be no smoke or abnormal smell.
- 2. There should be no abnormal sound.

#### 9.3 Check during operation and after use for;

- no fluid leakage,
- 2. no smoke nor abnormal smell,
- 3. no abnormal noise, and
- 4. no trace of Blood and/or Rinsing/Priming solution,



When a trace of Blood and/or Rinsing/Priming solution is found, wipe it off to prevent a trouble afterward, according to the instruction provided in "9.1.1Cleaning the Surface" of this Manual.

#### 9.4 Maintenance of the System

Safety-related inspection and maintenance of the MA-03 must be carried out only by person authorized by KANEKA PHARMA AMERICA LLC.

For further details on safety-related inspections and maintenance, see the MA-03 Maintenance manual.

When a trace of Blood and/or Rinsing/Priming solution is found, wipe it off to prevent a trouble afterward, according to the instruction provided in "9.1.1 Cleaning the Surface" of this Manual.



Safety-related inspection and maintenance of the system must be carried out in a safe place.

# 10. OPERATION SWITCH-OVER TIMETABLE

START 300 mL Whole Blood Circulation Only					
Treated Plasma (mL) Adsorption Column (Left)		Adsorption Column (Right)			
0	Adsorption (1)	500 mL	Standby		
500	Plasma Out	Re-Priming Solution 140 mL	,		
	Regeneration	Regeneration Solution 105 mL	Adsorption (2)	600 mL	
	Replacement	Replacement Solution 355 mL			
1,100			Plasma Out	Re-Priming Solution 140 mL	
	Adsorption (3)	600 mL	Regeneration	Regeneration Solution 105 mL	
			Replacement	Replacement Solution 355 mL	
1,700	Plasma Out Regeneration Replacement		Adsorption (4)		
2,300	Adsorption (5)		Plasma Out Regeneration Replacement		
2,900	Plasma Out Regeneration Replacement		Adsorption (6)		
3,500	Adsorption (7)		Plasma Out Regeneration Replacement		
4,100	Plasma Out Regeneration Replacement		Adsorption (8)		
4,700	Adsorption (9)		Plasma Out Regeneration Replacement		
5,300	Plasma Out Regeneration Replacement		Adsorption (10)		
5,900	Adsorption (11)		Plasma Out Regeneration Replacement		
6,500	Plasma Out Regeneration Replacement		Adsorption (12)		

note: In case the TR038 Abnormal conductivity alarm occurs, the value of the Treated Plasma at switching-over columns shifts larger because the machine treats an additional replacement up to maximum 300mL in the regenerating-column process and continues plasma treatment up to maximum 300mL.

#### 10. OPERATION SWITCH-OVER TIMETABLE

# 11. PUMP FLOW RATE REGULATION DURING OPERATION & RETURN OF THE MA-03

#### 11.1 Restrictive Pressure Limits Affecting Pump Flow Rate

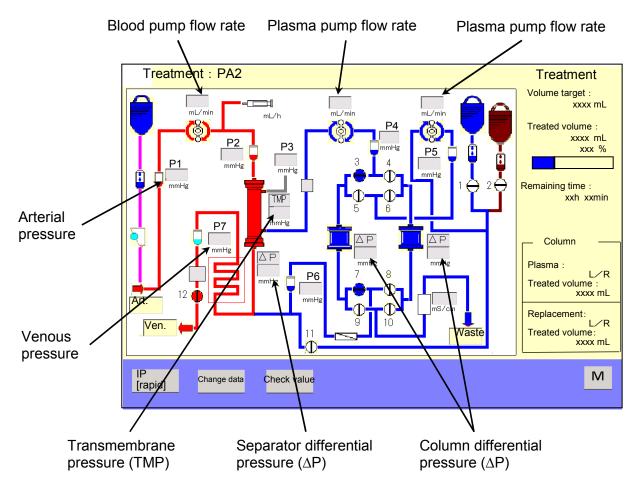
If any of the following conditions occurs, the affected pump will decelerate immediately and continue to decelerate until that condition is corrected (Table 11.1).

Table 11.1. Pump flow rate regulation during operation.

rable 11.1. Fulfip flow rate regulation during operation.			
Pump	Condition		
Blood pump	Arterial pressure 150 mmHg (blood flow rate > 20 mL/min.) note: -150 mmHg = -170 mmHg (alarm lower limit) + 20mmHg 70 mmHg (blood flow rate 20 mL /min.) note: This regulation works only in case the pump starts from 0mL/min  Venous pressure venous pressure alarm upper limit -20mmHg (set by operator)		
	Separator differential pressure 80 mmHg     note: 80 mmHg = 100 mmHg (alarm upper limit) - 20mmHg		
Plasma pump	<ol> <li>Transmembrane pressure (TMP) 40 mmHg         note: 40 mmHg = 60 mmHg (alarm upper limit) - 20mmHg</li> <li>Column differential pressure 100 mmHg         note: 100 mmHg = 120 mmHg (alarm upper limit) - 20mmHg</li> </ol>		
Replacement pump	Column differential pressure 100 mmHg     note: 100 mmHg = 120 mmHg (alarm upper limit) - 20mmHg		

#### 11.2 Restrictive Pressure Display For Pump Flow Rate

- 1. The Blood, plasma and/or replacement pump speeds may decrease from their set value, if the pressure exceeds the upper or lower alarm limit associated with each pump.
- 2. The following indication on the screen will turn to be yellow and blink depending on which restrictive pressure limit are exceeded.
  - · Blood pump flow rate
  - · Plasma pump flow rate
  - · Replacement pump flow rate
  - · Arterial pressure
  - · Venous pressure
  - Separator differential pressure (∆P)
  - · Transmembrane pressure (TMP)
  - Column differential pressure(∆P)



# 12. EXTRACORPOREAL VOLUMES

Below are the blood and plasma volumes for the LIPOSORBER® LA-15 System:

	Blood	Plasma
Tubing System for Plasmapheresis [NK-M3R(U)]	105	29
SULFLUX ® KP-05 Plasma Separator	55	75
LIPOSORBER® LDL Adsorption Column (AU)	0	140
Total Extracorporeal Volume (404 mL)	160	244

The plasma volume of the plasma separator is the value that the separator is filled with fluid.

#### 12. EXTRACORPOREAL VOLUMES

# 13. TECHNICAL INFORMATION OF THE MA-03

## 13.1 Specifications

Table 13.1 MA-03 Specifications.

Item	Specification
Weight	Approximately 77 kg (170 lbs.)
Storage and transportation temperature	-20 to 60°C

#### 13.2 Electrical Conditions

Table 13.2 Power specifications.

Phase	Voltage	Frequency	Current
Single	115 VAC ± 10%	50/60 Hz ± 1Hz	5A

Table 13.3. MA-03 setting ranges.

Table 10.0. Wit 00 detailing ranges.				
Item	Range			
Extracorporeal circulation volume	Approximately 400 mL (not adjustable)			
Treated plasma volume setting range	0 to 20,000 mL (1 ml increments)			
Whole blood flow rate setting range	7 to 200 mL /min			
Plasma flow rate setting range	0 to 40% of whole blood flow rate. (The minimum working flow rate of the plasma pump is 4 mL /min.)			
Venous pressure alarm setting range (upper limit)	0 to 300 mmHg			
Heparin infusion rate setting range	0.0 to 10.0 ml/h (0.1 mL /h increments)			
Blood warmer temperature setting range	35.0 to 39.0°C (0.1°C increments)			

## 13.3 Required Environmental Conditions

Use the MA-03 only in the following locations and environmental conditions.

#### Location

1. Operate the MA-03 under the following conditions:

Ambient temperature:15 to 35°C Relative humidity: 30 to 85% (No condensing)

- 2. Locate the MA-03 in a clean, dry area free of dust and moisture.
- 3. Avoid direct sunlight.
- 4. Place the MA-03 on a level floor and avoid vibration and shock.
- 5. Use only a hospital grade outlet when connecting the MA-03 electrical cord to the wall outlet.

# APPENDIX A Abbreviations and Symbols of the MA-03

## 1. Abbreviations and Symbols

#### 1.1 Abbreviations

AC : Alternating Current

AD : Air Detector

BLD : Blood Leak Detector

BP : Blood Pump

BSD : Blood/Saline Detector

CD : Conductivity Detector

DC : Direct Current

DD : Drip Detector

FD : Fluid Detector

IP : Infusion Pump

LD : Level Detector

P : Pressure Transducer

PA : Plasma Adsorption

PA2 : 2 Columns regeneration type Plasma Adsorption.

PH : Blood Warmer(Plate Heater)

PP : Plasma Pump

RP : Replacement Fluid Pump

TMP : Trans-Membrane Pressure

V : Valve

## 1.2 Symbols



Strictly observe the instructions regarding the equipment



Observe the instructions regarding the equipment

IPX1

Protection against dripping water (vertical drip)



Degree of protection against electric shock: Type B Applied part



Date of manufacture



Serial Number



**Alternating Current** 



Protective earth terminal (Grounding)



OFF (Turn off power to KANEKA MA-03)



ON (Turn on power to KANEKA MA-03)



ON (System-start switch)



Recyclable battery



Potential equalization conductor

APHERESIS MACHINE Apheresis Machine

# KANEKA PHARMA AMERICA LLC

546 Fifth Avenue, 21st Floor, New York, NY 10036 TEL: (212) 705-4340  $\,$ 

# LIPOSORBER® LA-15 SYSTEM

# Operator's manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)

#### **Humanitarian Use Device**

Authorized by Federal (USA) law for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

**Caution:** Federal law restricts this device to sale by or on the order of a physician.

### Important:

Be sure to carefully read this operator's manual before use.

Keep this manual by the machine for immediate reference.

This manual is applicable to the KANEKA MA-03 with the software version 1.2.

The software version is displayed on the KANEKA MA-03's screen.

KANEKA PHARMA AMERICA LLC NEW YORK, NY

#### **FOREWORD**

ABOUT THE LIPOSORBER® LA-15 SYSTEM OPERATOR'S MANUAL



This manual is applicable to the KANEKA MA-03 with the software version 1.2.

Confirm that the model of the machine and the software version described in this manual correspond to those in the machine to be used.

- 1. The model of the machine is described in the rating plate on the rear panel.
- 2. The software version is displayed on the LCD screen of the operation panel.

Maintenance mode menu screen is displayed on the LCD screen by touching the Maintenance mode key in the bottom area of the LCD screen.

Machine information screen opens by touching the Machine information key, and the software version is displayed on the LCD screen.

This Operator's Manual contains the information needed to operate the LIPOSORBER® LA-15 System correctly and safely. It is essential that you read this manual carefully and be sure you understand it before you operate the LIPOSORBER® LA-15 System. Pay particular attention to the Cautions and Warnings and to the items indicated by the safety alert symbol ...

#### • COMMENTS OR QUESTIONS

All reasonable efforts have been made to assure the accuracy of the contents of this Operator's Manual. If you have any comments or questions regarding this manual or any questions that are not answered in this manual, contact Kaneka Pharma America LLC.

Kaneka Pharma America LLC 546 Fifth Avenue; 21st Floor New York, NY 10036

Telephone: (212) 705-4340 Fax: (212) 705-4350

#### • ABOUT THE SAFETY ALERT SYMBOL

The safety alert symbol  $\triangle$  identifies situations that could be dangerous to the operator or the patient and directs your attention to the proper operation of the Apheresis Machine KANEKA MA-03 (hereinafter the MA-03). Read and understand each Warning, Caution and Notice thoroughly. See the next page of this manual for an explanation of these safety alerts.

This manual is copyrighted by Kaneka Pharma America LLC and no part of it should be reprinted without Kaneka Pharma America LLC's prior permission.

This operator's manual is intended to be a reference for proper and safe operation of the MA-03. In no way is this manual intended to be a step-by-step guide in the actual decisions regarding the treatment of the patients.

For proper and safe operation, be sure to carefully read this operator's manual before use. Keep this manual by the machine for immediate reference.

#### Symbols and Remarks for Safety

In this manual and on each MA-03, the following safety symbols and remarks are shown for safe and proper use of the equipment.

The meanings of the symbols are as follows.

Familiarize yourself with the meanings of the symbols before reading the text of the manual.



DANGER indicates an imminently hazardous situation which, if not avoided, will result in death or serious injury.



WARNING indicates a potentially hazardous situation which, if not avoided, may result in death or serious injury.



CAUTION indicates a potentially hazardous situation which, if not avoided, may result in minor or slightly injury.



NOTICE indicates practices you must know when operating the machine, although the situation may not be as serious as those mentioned above.

#### • COMPONENTS

The LIPOSORBER® LA-15 System is an integrated, automated extracorporeal blood processing system that includes the following 3 disposables and a control/monitor machine:

LIPOSORBER® LA-15 LDL Adsorption Column set (disposable) consisting of two columns, each containing 150 ml of dextran sulfate cellulose adsorbent;

SULFLUX® KP-05 Plasma Separator (disposable) containing hollow fibers made of polyethylene coated by an ethylene-vinyl alcohol copolymer;

Tubing System for Plasmapheresis (NK-M3R(UL)) (disposable); and

the Apheresis Machine KANEKA MA-03, which monitors and controls the LDL-apheresis procedure.

#### • PRINCIPLES OF OPERATION

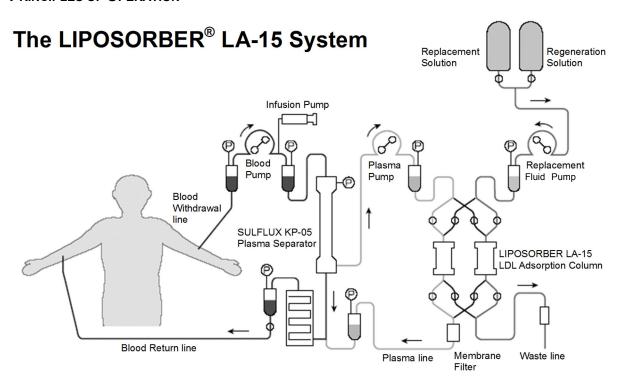


Figure A. LIPOSORBER® LA-15 System overview.

As illustrated in Figure A, the patient's blood is withdrawn via a venous access connected to the blood withdrawal line and enters the plasma separator. As blood flows into the top of the separator, through the hollow fibers, plasma is separated and exits from the separator side outlet. The remaining blood, including red and white blood cells and platelets, exits from the separator bottom outlet. The cell-free plasma enters the top inlet of one of the two LDL adsorption columns. As the plasma passes through the column, the apolipoprotein B-containing lipoproteins - LDL, VLDL, and Lp(a) - are selectively adsorbed in the column. There is minimal effect on HDL and other plasma components. The LDL-depleted plasma exits the adsorption column bottom outlet, flows through the membrane filter, is recombined with the blood cells exiting the separator bottom outlet and is returned to the patient via venous access.

When the first 500 ml of plasma has been treated with the left column, the MA-03 automatically switches the plasma flow to the right column. At this point, the plasma exiting the plasma separator flows into the right column, while the plasma remaining in the left column is pushed out with 140 ml of replacement solution (Lactated Ringer's Injection, USP) and returned to the patient.

When recovery of the plasma from the left column is completed, the plasma return line is switched over from the left column to the right column, enabling the plasma in the right column to return to the patient. Throughout this column switch-over operation, the replacement fluid pump is automatically operated at the same speed as the plasma pump. The replacement solution during each switch-over is not returned to the patient.

While the right column is still treating plasma, the left column is rinsed with 105 ml of regeneration solution (5% Sodium Chloride Injection, USP), and its original adsorption capacity is restored. Along with the regeneration solution, apolipoprotein B-containing lipoproteins LDL, VLDL, and Lp(a) are flushed from the column through the waste line into the waste bag. When elution is completed, 355 ml of replacement solution is pumped through the column to rinse out the regeneration solution completely and re-prime the column. The column is now ready for the next cycle of adsorption.

Subsequent switch-over and regeneration cycles are repeated every time 600 ml of plasma has been treated by one of the two LDL adsorption columns, allowing continuous LDL-apheresis until the predetermined plasma volume has been treated. The first switch-over occurs at 500 ml because initial levels of LDL, VLDL, and Lp(a) are higher in the first cycle.

The tubing system, plasma separator and two LDL adsorption columns, are intended for single use only. All disposables must be discarded after each procedure.

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### **APPENDIX A**

Abbreviations and Symbols of the MA-03

## 1. INTRODUCTION

This operator's manual is intended to be a reference for proper and safe operation of the Apheresis Machine Kaneka MA-03. In no way is this manual intended to be a step-by-step guide in the actual decisions regarding the treatment of the patients.

For proper and safe operation, be sure to carefully read this operator's manual before use. Keep this manual by the machine for immediate reference.

## 1.1 Description

The LIPOSORBER® LA-15 System is an integrated, automated extracorporeal blood processing system that includes the following 3 disposables and a control/monitor machine:

LIPOSORBER® LA-15 LDL Adsorption Column set (disposable) consisting of two columns, each containing 150 ml of dextran sulfate cellulose adsorbent;

SULFLUX® KP-05 Plasma Separator (disposable) containing hollow fibers made of polyethylene coated by an ethylene-vinyl alcohol copolymer;

Tubing System for Plasmapheresis (NK-M3R(UL)) (disposable); and

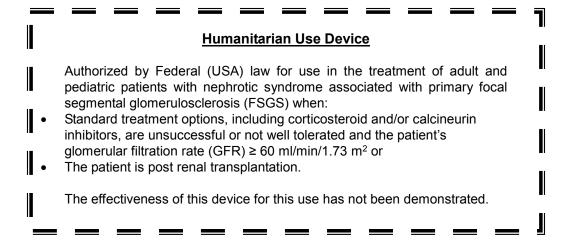
the Apheresis Machine KANEKA MA-03, which monitors and controls the LDL-apheresis procedure.

All of the above components are authorized by Federal law for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS).

### Caution: Federal law restricts this device to sale by or on the order of a physician.

This system may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended at all times by a physician or qualified health-care professional adequately trained in all aspects of the procedure. All physicians and medical personnel utilizing the LIPOSORBER® LA-15 System will be required to have completed an appropriate training program.

### 1.2 Indications for Use



The LIPOSORBER® LA-15 System is indicated for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis when:

- Standard treatment options, including corticosteroids and/or calcineurin inhibitor treatments, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

### 1.3 Contraindications

The LIPOSORBER® LA-15 System must not be used in:

- 1. patients who have been treated with angiotensin-converting enzyme (ACE) inhibitors within the past 24 hours;
  - Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER® LA-15 LDL Adsorption Column under concomitant ACE inhibitor medication. The risk of an anaphylactoid reaction may be minimized by withholding the administration of ACE inhibitors for approximately 24 hours before each LDL-apheresis procedure. The time period to withhold ACE inhibitors should be prolonged, if determined by the treating physician, considering each individual's renal function and the biological half-life of the ACE inhibitor currently in use. If required, ACE inhibitor administration may be resumed on the day of the apheresis treatment but only after the apheresis treatment is complete.
- 2. patients for whom adequate anticoagulation cannot be achieved, such as those with severe hemophilia, severe hemorrhage diathesis, severe gastrointestinal ulcers, or who are receiving vitamin K antagonist medications after surgery;
- patients for whom extracorporeal circulation therapy with the LIPOSORBER <sup>®</sup> LA-15 System cannot be tolerated such as those with severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, acute apoplexy, or severe uncontrollable hypertension or hypotension; and
- 4. patients with hypersensitivity to dextran sulfate cellulose, heparin or ethylene oxide.

### 1.4 Patient Selection

The following patients may benefit from the LIPOSORBER® LA-15 System. The following are intended only as guidelines for appropriate patient selection:

- Adult and pediatric patients with GFR > 60 ml/min/1.73 m<sup>2</sup> and a history of primary FSGS accompanied by refractory or recurrent nephrotic syndrome defined as:
  - Patients unresponsive to standard corticosteroid and/or calcineurin inhibitor therapy for at least 8 weeks resulting in failure to achieve complete or partial remission

or

 Patients intolerant to standard therapies due to severe side effects which negatively affect quality of life without providing an acceptable level of clinical benefit.

or

Patients in whom standard therapies are contraindicated.

OR

• Adult and pediatric post renal transplantation patients with nephrotic syndrome associated with primary FSGS.

## 1.5 Warnings

- 1. Before using the LIPOSORBER® LA-15 System, carefully review the instructions for use provided for each of the disposables and this Operator's Manual. Persons performing the procedures must be qualified to perform extracorporeal procedures, and have completed the required training program. Users should follow all operating or maintenance procedures published by Kaneka Pharma America LLC and use only the disposable device components recommended by Kaneka Pharma America LLC. Failure to do so may result in injury or loss of life.
- 2. **LDL-apheresis treatment of patients who have taken any antihypertensive drugs within 24 hours of treatment may cause hypotension in such patients.** When clinically feasible, patients should not receive antihypertensive drugs during the 24-hour period prior to undergoing the LDL-apheresis procedure. Before each treatment, physicians should determine when patients took their last dose of such medication.
- 3. The storage and use of this disposable device other than in accordance with the instructions published by Kaneka Pharma America LLC or the use of disposable device components not recommended by Kaneka Pharma America LLC may result in serious patient injury or loss of life. The manufacturer and distributor(s) of the disposable devices will not be responsible for patient safety if the procedures to operate and maintain the LIPOSORBER® LA-15 System are other than those specified in the instructions for use and this Operator's Manual.
- 4. During an LDL-apheresis procedure, 0.9% Sodium Chloride Injection, USP, 5% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP, and Heparin Sodium Chloride Injection, USP, are used. Carefully identify each solution and ensure that it is properly connected to the LIPOSORBER® LA-15 System. Using the incorrect solution may result in serious injury or possible death.
- 5. The disposables are **intended for use in a single procedure only. Never reuse.**Discard the disposables after each use.
- 6. The LIPOSORBER® LA-15 System may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended to at all times by a physician or qualified health-care professional adequately trained in all aspects of the procedure.
- 7. Rinsing and subsequent priming of the fluid pathway of the disposables with appropriate solutions are necessary before commencing the procedure. Because air bubbles in the disposables may lead to complications such as coagulation of plasma and impairment of performance, give full attention to measures that will prevent air bubble migration into the disposables during rinsing and priming.
- 8. While operating, the differential pressure across the LIPOSORBER® LA-15 LDL Adsorption Column must be under 100 mmHg, and the transmembrane pressure (TMP) of the SULFLUX® KP-05 Plasma Separator must be under 60 mmHg. If either an extreme rising of the differential pressure across the column or extreme rising of the TMP occurs, the blood flow rate and/or plasma separation rate should be lowered appropriately or even stopped if necessary.

- 9. Citrate preparation (ACD) should never be used as an anticoagulant in the system. The LIPOSORBER® LA-15 System is designed solely for treatment using heparin as an anticoagulant. Anticoagulation is required to prevent thrombus formation from occurring within the extracorporeal circuit. Anticoagulation with too much heparin is associated with an increased risk of bleeding for the patient, especially after the procedure. In order to reduce the risk of bleeding, the puncture sites should be sufficiently compressed so that bleeding is stopped. (See Section 1.7 Adverse Events) In some patients the potential for development of a coagulopathy extending several days post-therapy may exist. In addition to adjusting heparin dosage based on clinical observation during and after the apheresis procedure, Activated Clotting Time and/or partial thromboplastin time (PTT) values may be used. (See Section 1.9.2 Instructions for Use regarding "Determining Heparin Dosage")
- 10. To minimize the risk of air embolism, the return tubing line must be connected to the air bubble detector.
- 11. No chemicals or solvents are to be used either inside or outside of the disposables.
- 12. Due to the risk of reduction of blood pressure with the LIPOSORBER® LA-15 System, extra caution should be exercised in use of the device in patients with systolic and/or diastolic blood pressure ≤ 5<sup>th</sup> percentile for age, gender and height.
- 13. Use special caution in patients where the extracorporeal volume of approximately 400 ml potentially will exceed 10% of the patient's blood volume. Such patients are at higher risk of experiencing hypovolemia, which is sometimes followed by hypotension.
- 14. In case of a power failure or system shutdown, terminate the procedure immediately according to the instructions provided in Section <u>7.6 Manual Blood Return</u> of this Operator's Manual.
- 15. The safety of LDL-apheresis treatment with the LIPOSORBER® LA-15 System occurring more than twice a week or for treated volumes larger than 60mL/kg patient plasma volumes in FSGS has not been established.
- 16. Do not apply whole blood directly to the LIPOSORBER® LA-15 LDL Adsorption Column. The column is designed for perfusion of plasma only.
- 17. Make sure that the plasma flows in the direction of the arrow on the label of the LIPOSORBER® LA-15 LDL Adsorption Column.

### 1.6 Precautions

- 1. The need for the administration of angiotensin receptor blockers (ARBs) prior to the treatment on the day of the apheresis treatment should be determined by the treating physician. If the treating physician determines that it is not necessary, the patient should not take ARBs on the day of the apheresis treatment until the apheresis treatment is completed in order to minimize the risk of a hypotensive reaction during the extracorporeal therapy.
- 2. Medical personnel should monitor the patient for adverse symptoms at all times during treatment and should be trained as to the protocol for responding with appropriate interventions. (See Section 1.7 Adverse Events)
- 3. All connections of the extracorporeal circuit should be checked carefully prior to initiating and during the procedure. Avoid unnecessary kinking of the tubing lines and the patient's vascular access devices at all times.
- 4. The transducer protectors must be attached and locked to the machine and tubing lines. Strict aseptic technique should be used during this and all procedures. After the completion of the procedure, properly dispose of all used and unused transducer protectors. Do not reuse.
- 5. Each tubing line must be properly connected and cleared of air, prior to the start of Rinse. Do not allow air to be trapped in the set. Puncturing tubing lines may cause air embolism.
- 6. Drip chambers in the extracorporeal circuit should be kept at least 2/3 to 3/4 full and monitored at all times in order to decrease the risk of air embolism.
- 7. The fluid circuit of this system is intended to be sterile and nonpyrogenic. Aseptic handling techniques are necessary to maintain these conditions. Prior to use, carefully examine the packaging of the disposable device components to ensure that it is intact and undamaged. Do not use a disposable product if the package, sterile bag, protective cap or the product itself is not intact or is damaged. Do not open the sterile bags containing the disposables until immediately prior to use.
- 8. The safety and probable benefit of LDL-apheresis using the LIPOSORBER® LA-15 System in FSGS have not been established for: (1) patients less than 21 kg in body weight; (2) patients less than 5 years of age; (3) patients with certain cardiac impairments such as uncontrolled arrhythmia, unstable angina, decompensated congestive heart failure or valvular disease; and (4) patients with thyroid disease or liver abnormalities.
- The safety and probable benefit of LDL-apheresis using the LIPOSORBER® LA-15
   System in FSGS have not been established for pregnant women or for women during the
   lactation period, e.g. the effect of treatments on folic acid levels has not been
   determined.
- 10. Closely monitor patient clotting time periodically during the procedure to ensure that an adequate level of anticoagulation is maintained.
- 11. Instructions for heparin administration should be followed as stated in the guidance provided by the manufacturer in this Operator's Manual. The amounts of heparin outlined in this Operator's Manual are intended as general suggestions. The exact amount, frequency and method of administration of heparin are the sole responsibility of the prescribing/attending physician and should be selected based on the individual patient's clinical condition.

- 12. Physicians and operators should follow the OSHA and the CDC/ACIP Adult Immunization Guidelines for Hemodialysis Patients. It is recommended that patients be screened for Hepatitis B and other infectious diseases; however, due to possible exposure to hepatitis virus, human immunodeficiency virus, and other infectious agents when handling extracorporeal blood circuits, blood or blood products, universal precautions should be taken at all times to prevent the exposure to and transmission of such agents.
- 13. When disposing of the disposable device components and wastes, comply with all local requirements and the policies of the facility regarding precautions for and prevention of infection and environmental pollution.
- 14. In transporting and storing the disposables, handle with care. Store all disposables in a clean and secure area at room temperature, avoiding exposure to direct sunlight, high humidity or excessive vibration. Handle the disposables with care to avoid dropping or other sudden impacts and never allow them to freeze. Do not use disposables which may have been dropped, damaged or frozen.
- 15. The disposables must never be used after the expiration date.
- 16. The LIPOSORBER® LA-15 System includes a blood warmer with a temperature setting range of 35-40 °C. It is recommended that the blood warmer be set at a temperature between 36-38 °C in order to avoid significant decreases in blood temperature during extracorporeal circulation.
- 17. Anemia may be minimized by the appropriate use of iron supplements.

### 1.7 Adverse Events

Adverse events that may be associated with the use of the LIPOSORBER® LA-15 System in FSGS include, but are not limited to, those listed in the following paragraphs. If a patient experiences an adverse reaction during a procedure, the physician should stop the procedure until the cause of the reaction has been determined and the patient's condition stabilized. The physician should determine all medical responses to adverse reactions based upon the individual patient's physical condition.

- 1) Death
- 2) Cardiac: Various abnormal heart rhythms may develop including bradycardia, tachycardia, and other arrhythmias. Myocardial infarction is another potential adverse cardiac event. If these are detected by vital sign monitoring, physical examination, or electrocardiography, immediate assessment and continued monitoring is essential.
- 3) Thrombocytopenia
- 4) Catheter-related adverse events: Use of the device requires a central venous access (catheter) for children and for some adults given their small venous caliber. Infection of the catheter may occur due to exit site infection, catheter-related bloodstream infection (CRBSI), improper use of the catheter, or internal catheter infection. Aseptic technique is required for catheter use. If an infection or bacteremia is suspected, culture of the catheter ports, in conjunction with peripheral culture (optional), is required. Antibiotic therapy should be provided according to physician discretion. Also, there are other adverse events associated with catheter use (e.g., hemothorax, pneumothorax, blood loss, arterial puncture, superior vena cava syndrome, arrhythmia, central venous stenosis, thrombosis and loss of potential fistula access).
- 5) Hypersensitivity (anaphylactoid) reaction: Use of angiotensin-converting enzyme inhibitors (ACEi) within 24 hours of therapy with the device can cause an increase in bradykinin levels, resulting in severe hypotension. ACE inhibitors should not be taken within 24 hours of therapy with the device.
- 6) Nausea and Vomiting. The procedure should be stopped and the etiology of the nausea and vomiting investigated (e.g., hypotension).
- 7) Reduction in Vitamin E level
- 8) Transient decrease in serum protein and albumin level
- 9) Hypotension: The procedure should be stopped, and the patient should be placed in the Trendelenburg position and/or receive a fluid challenge. If the hypotension persists, the procedure should be terminated. Note: For an "anaphylactoid" reaction, administration of epinephrine, sympathomimetic drugs, prednisolone, anti-histamines, and/or calcium have been reported by clinicians as effective interventions.
- 10) Abdominal symptoms. Patients may exhibit nausea, vomiting abdominal discomfort. These events should be addressed with conservative management and supportive care. The procedure should be stopped and the etiology of the nausea and vomiting investigated (e.g., hypotension).
- 11) Flushing/blotching: Check vital signs and reduce the blood flow rate. If symptoms are persistent or repetitive, consider the administration of diphenhydramine (e.g., Benadryl).

- 12) Angina/chest pain: The procedure should be stopped and medical therapy instituted at the discretion of the physician. If the angina persists, the procedure should be terminated.
- 13) Fainting/lightheadedness: See hypotension.
- 14) Anemia: May be minimized by the appropriate use of iron supplements.
- 15) Prolonged bleeding (at cannulation site after removing venous cannulae): Direct manual pressure should be applied until the bleeding stops. If prolonged bleeding occurs (in excess of 20 minutes), adjustment of the heparin dosing may be necessary. It is recommended that, during the subsequent procedure, the heparin dose be reduced and monitored by Activated Clotting Time (ACT). Repetitive LDL apheresis treatment may affect the patient's clotting time. Therefore, a periodic check, of other relevant coagulation parameters is recommended, including the number of thrombocytes and the fibrinogen concentration, in order to ensure that these parameters are sufficient to maintain adequate coagulation.
- 16) Hemolysis: as evidenced by discoloration of plasma or hemolysis as Indicated by activation of the blood leak detector alarm of the MA-03. If either indicator of hemolysis occurs, the procedure should be terminated and the patient's hematocrit, urine output and kidney function monitored.
- 17) Device malfunction: The system contains various components, including LDL apheresis columns (2), plasma separator, tubing system, and an electronic control unit. System malfunction may occur due to any of these components. If system malfunction occurs, the patient's vital signs and clinical status should be monitored immediately and repeatedly. It may be necessary to suspend treatment if the patient develops symptoms or if the problem cannot be readily solved.
- 18) Vertigo
- 19) Diaphoresis
- 20) Urticaria: Mild discomfort may occur requiring supportive care. Vital signs and physical examination of the patient are required in order to assess if urticaria is a component of a more severe, generalized reaction to the therapy. Specific associated symptoms, including, but not limited to, difficulty breathing, chest pain, and dizziness should be addressed by the physician.
- 21) Shivering
- 22) Headaches

### 1.8 Clinical Data

Clinical data to support the safety and probable benefit of LIPOSORBER® LA-15 System for FSGS can be divided to pre-transplant FSGS and post-transplant FSGS.

### **1.8.1 Adults**

Published Clinical Studies of LIPOSORBER® LA-15 System Treatment for Patients with Nephrotic Syndrome (NS) and FSGS in adults are summarized in the table below.

Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre- transplant or Post- transplant
Muso 2015 [1] Muso 2015 [2]	44 (26 with FSGS)	Prospective Multicenter Single arm	Immediate to 2 years after treatment	Urinary Protein (UP) decreased from 6.28 ± 2.96 to 3.46 ± 3.34 g/day. 21/44 patients (48%) had a favorable 2-years outcome.	Pre- transplant
Muso 2001 [3] Muso 1999 [4]	17 (14 with FSGS)	Prospective Multicenter Controlled	Immediate to 2 years after treatment	UP decreased from 6.2 ± 3.3 to 2.7 ± 2.7 g/day.  The rate of achieving complete or incomplete remission was 71%.  As for the 2-years outcomes, 13/17 patients (76%) maintained UP <1.0 g/day.	Pre- transplant
Yokoyama 2002 [5]	6 (2 with FSGS; 1 treated with LIPOSO RBER®)	Prospective Single Center	Unknown	This was a prospective study of the effects of lymphocytapheresis in treating various forms of NS in 6 patients. One patient with FSGS failed to respond to one month of LIPOSORBER® treatment.	Pre- transplant
Nakamura 2006 [6]	8 FSGS	Prospective Single Center	2 weeks	UP decreased from 8.8 ± 4.2 g/day to 2.0 ± 1.2 g/day.	Pre- transplant

Muso 2007 [7]	No. of Patients 41 FSGS	Study Design Retrospective	Length of Follow-up  5 years	At 1 month after LDL apheresis UP was significantly decreased.  Remission of nephrotic syndrome was observed	Pre- transplant or Post- transplant Pre- transplant and Post- transplant
				in 18/29 patients (62%) followed at 2 years and 13/15 patients (86%) followed at 5 years.	
Case Studie			T	T	
Masutani 2005 [8]	1 FSGS	Case Report	1 year	LIPOSORBER® in conjunction with drug treatment resulted in reduction of UP from 6.8 g/day to 2.0 g/day.	Post-trans plant
				Incomplete remission had been maintained for more than 1 year.	
Miura 2009 [9]	1 FSGS	Case Report	40 days	Six cycles of hemodialysis were performed in conjunction with 4 cycles of LIPOSORBER® treatment. UP and serum creatinine levels recovered to normal values, and UP became undetectable by 40 days post-treatment.	Pre-transp lant
Miyazono 2008 [10]	1 FSGS	Case Report	Unknown	After 6 treatment sessions, the patient's UP decreased to non-nephrotic level. Furthermore, the patient's hypoproteinemia improved and renal function returned to normal. Although the patient experienced a relapse of nephrotic syndrome, 6 more sessions of LIPOSORBER® treatment brought the UP down to 0.8 g/day.	Pre-transp lant

Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre- transplant or Post- transplant
Tsukada 2006 [11]	1 FSGS	Case Report	Unknown	The patient underwent 8 sessions of treatment using LIPOSORBER®, which resulted in the reduction of the UP level and improvement of renal functions.	Post-trans plant
Haikal 2016 [12]	1 FSGS	Case Report	5 months	Partial remission sustained 5 months post therapy	Pre-transp lant

### 1) Pre-transplant FSGS

(i) Muso et al. (2001) [3]: This study describes the comparison of efficacy between the treatment with the LIPOSORBER® LA-15 System in combination with steroids (LDL-A group) and that with steroids only (steroid monotherapy (SM) group) for patients with nephrotic syndrome who did not respond to full-dose (prednisolone, daily 1 mg/kg b.w.) therapy of 1-month duration under the fixed treatment protocol. The LDL group consisted of 17 patients (FSGS: 14, minimal change nephrotic syndrome (MCNS): 3) who were treated with the LIPOSORBER® LA-15 System. Treatments were performed twice a week for 3 weeks followed by weekly treatment for 6 weeks. The SM group included 10 patients (FSGS: 9, MCNS: 1) who were treated only with continuous full-dose steroids.

#### Results

### Effectiveness:

- Total cholesterol (TC) level in the LDL-A group was significantly decreased after the treatment (337  $\pm$  118 to 242 $\pm$ 45.2 mg/dL, p=0.006), whereas decrease of TC level in the SM group was not significant (448 $\pm$ 106 to 366 $\pm$ 159 mg/dL, p=0.169).
- Hypoalbuminemia significantly improved in the LDL-A group (2.7±0.7 to 3.1±0.7 g/dL, p=0.014), while almost no change was noted in the SM group (2.8±0.4 to 2.9±0.7 g/dL, p=0.822).
- Proteinuria was significantly ameliorated in the LDL-A group (6.2±3.3 to 2.7±2.7 g/day, p=0.0008), while significant amelioration of proteinuria was not observed in the SM group (8.7±4.0 to 8.2±7.7 g/day, p=0.85).
- Average duration needed for a decrease of urinary protein to <3.5 g/day was significantly shorter in the LDL group than in the SM group (14.7±19.6 days vs 47.8±6.9 days, p=0.002).
- At the end of the treatment period, 9 patients (52%) in the LDL-A group achieved urinary protein level <1.0 g/day, whereas only 1 patient (10%) showed the same level in the SM group.
- As for the long-term outcomes (2 years after the end of the treatment period), 13 out of 17 patients (76%) maintained urinary protein level <1.0 g/day in the LDL-A group, compared to only 2 in 9 patients (22%) in the SM group.

#### Safety:

• The incidence of adverse events was not reported.

#### Conclusion

Superiority of therapeutic efficacy of the treatment with the LIPOSORBER® LA-15 System in combination with steroids to that with steroids alone was demonstrated in controlled study.

This study was a follow-up of the multicenter study reported by Muso et al (Kidney Int) in 1999. In this study, the authors did not report any adverse events.

Summary: Among the 17 patients with FSGS, short-term and medium-term efficacy data were provided compared to controls. Adverse events were not mentioned in the report.

(ii) Nakamura et al. (2006) [6]: This study investigated the effect of LIPOSORBER® LA-15 System in treating FSGS as part of a larger study to determine whether the levels of urinary liver-type fatty acid-binding protein (L-FABP) are associated with the severity of nephrotic syndrome. At the beginning of the study, all FSGS patients received 60 mg/day prednisone for 6 months, followed by either cyclophosphamide or mizoribine for another 6 months. Treatment with LIPOSORBER® LA-15 System was performed in 8 patients with drug-resistant FSGS twice a week for 3 weeks, then once a week for 6 weeks. In each 3-hour treatment session, 3000-4000 mL of plasma were treated. Renal function in terms of daily urinary protein excretion and serum creatinine levels were measured before the start of treatment and 2 weeks after the final treatment session.

#### Results

#### Effectiveness:

- Comparing the clinical parameters before and after the treatment, urinary protein and serum creatinine decreased significantly from 8.8  $\pm$  4.2 g/day to 2.0  $\pm$  1.2 g/day (p < 0.01) and from 123.8  $\pm$  26.5  $\mu$ mol/L to 97.2  $\pm$  17.7  $\mu$ mol/L (p < 0.05), respectively, and total protein increased from 40  $\pm$  8 g/L to 60  $\pm$  9 g/L (p < 0.01).
- In addition, serum level of L-FABP decreased from 122.6  $\pm$  78.4  $\mu$ g/gCr to 64.4  $\pm$  43.8  $\mu$ g/gCr (p < 0.05).

#### Safety:

 The article did not report any adverse events associated with LIPOSORBER® LA-15 System.

#### Conclusion

This study demonstrated that LDL apheresis therapy with LIPOSORBER® LA-15 System ameliorated proteinuria, hypoproteinemia, and renal function in drug-resistant FSGS.

This was a prospective study. Among the 8 patients with FSGS, encouraging short-term efficacy data were provided. A control arm was not included in this study. Adverse events were not mentioned in the report.

(iii) Muso et al. (2015) [1]: The investigators conducted a prospective, observational, multi-center cohort study (POLARIS study). In the POLARIS study, patients with nephrotic syndrome who did not respond to primary medication were registered before starting the treatment with LIPOSORBER® LA-15 System and clinical effectiveness and safety were examined. A total of 58 patients (who underwent 64 treatments) were registered in the study. Of the 64 treatment regimens, 17 were excluded for various reasons, leaving 47 treatment regimens for 44 patients available for analysis. As for FSGS, 23 patients were registered and underwent a total of 26 treatments. Clinical data were collected at baseline and after treatment with LDL-apheresis based on 24-hour urinalysis. Lipid profiles and clinical parameters were compared between before and after the treatment.

#### Results

#### Effectiveness:

- TC and LDL cholesterol (LDL-C) levels were significantly decreased after the treatment (331.10  $\pm$  113.25 to 210.38  $\pm$  77.4 mg/dL; p<0.01, 205.86  $\pm$  100.to 84 92.37  $\pm$  56.64 mg/dL; p<0.01, respectively), whereas the changes of triglyceride (TG) and HDL-cholesterol (HDL-C) were not significant (262.74  $\pm$  155.17 to 241.30  $\pm$  182.14 mg/dL; n.s., 69.49  $\pm$  22.58 to 73.64  $\pm$  23.40 mg/dL; n.s.).
- Hypoproteinemia (serum protein), hypoalbuminemia (serum albumin), and proteinuria (urinary protein) were significantly ameliorated immediately after treatment (4.42 ± 0.69 to 4.68 ± 0.81 g/dL; p<0.05, 2.15 ± 0.63 to 2.63 ± 0.79 g/dL; p<0.01, and 6.28 ± 2.96 to 3.46 ± 3.34 g/day; p<0.01, respectively). In addition, renal function (creatinine clearance) significantly improved immediately after treatment (58.59 ± 41.35 to 65.11 ± 41.39 mL/min; p<0.05).</li>
- Serum levels of fibrinogen and thrombin-antithrombin III complex (TAT) level were significantly reduced (374.46 ± 130.04 to 297.92 ± 108.87 mg/dL; p<0.01, 16.39 ± 33.60 to 12.21 ± 34.10 ng/mL; p<0.05, respectively) suggesting that treatment with LIPOSORBER® LA-15 System exerts anticoagulation activity.</li>

#### Safety:

• The incidence of adverse events was not reported.

### Conclusion

LDL apheresis therapy with LIPOSORBER® LA-15 System rapidly ameliorated symptoms of nephrotic syndrome, i.e., proteinuria and hypoproteinemia, in more than half of the patients who failed to respond to primary medication.

This was a short-term study.

The endpoints were:

- Complete remission: Urinary Protein (UP) = undetectable
- Incomplete Remission I: UP < 1.0g/day</li>
- Incomplete Remission II: 1.0 g ≤ UP < 3.5 g/day</li>
- No effect: UP ≥ 3.5 g/day

In this study, complete or incomplete remission were considered favorable outcomes.

The average number of apheresis sessions was 9.6/patient. An average of 3.5 L of plasma was treated per session. Among the 44 patients, FSGS was the diagnosis in 23 (52.3%) of the patients.

(iv) <u>Muso et al. (2015) [2]:</u> The long-term (2 years) outcome of the POLARIS cohort was investigated for the 44 subjects. Of the 58 patients who were registered in the POLARIS study, 5 were excluded from the study because of protocol violation or inadequate data collection, 6 were lost to follow up, and 3 died during the follow-up period, thus leaving 44 subjects eligible for analysis at two years. As for primary diseases of the subjects, FSGS was found in the majority of cases, presenting in 28 subjects (63.6%).

#### Results

### Effectiveness:

- Twenty-one (21) of the 44 subjects (47.7%) had a favorable outcome, with 11 subjects (25%) in complete remission (defined as urinary protein undetectable) and 10 subjects (22.7%) in incomplete remission I (defined as urinary protein level < 1.0 g/day). Twenty-three (23) subjects (52.3%) had an unfavorable result, with 11 (25%) in incomplete remission II (defined as 1.0 g/day < urinary protein < 3.5 g/day) and 12 (27.3%) with no effect (defined as urinary protein level > 3.5/day).
- An analysis was performed of the factors affecting outcome. The authors found that the urinary protein level post-treatment was strongly associated with 2-year outcome (p < 0.001). For subjects with favorable outcomes, the urinary level after treatment was  $1.68 \pm 1.76$  g/day compared to  $6.18 \pm 3.24$  g/day for subjects with unfavorable outcomes.
- Improvement of parameters representing disease conditions of nephrotic syndrome, including serum albumin, eGFR, urinary protein and total and LDL cholesterol were all significantly associated with favorable outcome. This suggests that an early rapid alleviation of nephrotic syndrome by LDL-apheresis contributes to a favorable outcome.

#### Safety:

 No adverse event associated with LIPOSORBER® LA-15 System was reported in this report.

#### Conclusion

The POLARIS study demonstrated that LDL apheresis therapy with LIPOSORBER® LA-15 System ameliorates nephrotic conditions and that the therapeutic efficacy of LDL apheresis was largely maintained for two years.

During the time from the short- to long-term POLARIS study, 3 subjects died of diseases unrelated to NS (cerebral infarction, lung cancer and pneumonia). Given the variety of histological diagnoses in the patients included in the study, it was challenging to ascertain the outcomes for patients with FSGS versus those with other diseases. That said, the study does report that urine protein levels decreased significantly and similarly for patients with/without FSGS and this study provides reasonable assurance of efficacy of the device in about 50% of patients with FSGS.

### 2) Post-transplant FSGS

Muso et al. (2007) [7]: This study describes 41 patients with refractory FSGS. The study population included a sub-set of 7 patients who developed recurrent FSGS after undergoing renal transplantation. The study was intended to evaluate the long-term outcome of LDL apheresis in patients with FSGS.

The study included the change in lab values (e.g., serum protein, serum albumin, proteinuria) at 1 month after treatment and measured the number of patients achieving remission of nephrotic syndrome at 2 and 5 years after LIPOSORBER® treatment. Although the investigators did not indicate that any of the patients included in the analysis were children, the results can be used to assess effectiveness in children as the course of the disease is sufficiently similar in both adults and children.

The criteria used to assess clinical response were:

- Remission of nephrotic syndrome (NS)
  - o Complete remission
  - Type I incomplete remission: proteinuria negative or < 1.0 g/day and serum albumin > 3.0 g/dL
  - Type II incomplete remission: proteinuria < 3.5 g/day but serum albumin</li>
     3.0 g/dL

#### Results

#### Effectiveness:

- At 1 month after LDL apheresis total serum protein and albumin increased significantly and proteinuria was significantly decreased.
- Remission of nephrotic syndrome was observed in 18/29 patients followed at 2 years (62%).
- Remission of nephrotic syndrome was observed in 13/15 patients followed at 5 years (86%).

The seven post-transplant patients were included in the 41 patients analyzed at 1 month. The authors did not analyze the data collected from pre- and post-transplant patients separately. Instead, the authors state that the exclusion of the post-transplant patient data did not impact the data trend or significance of the results, indicating that the post-transplant data were similar as a group to the pre-transplant patients in terms of increase in serum protein and albumin and decrease in proteinuria. The authors did not indicate the number of post-transplant patients included in the 2 and 5 years follow-up.

#### Safety

• The incidence of adverse events was not reported.

### Conclusion

The authors conclude that early administration of LDL-apheresis after the onset of nephrotic syndrome associated with FSGS provides a good long-term outcome.

This was a retrospective study. Patients had drug-resistant (persistence of proteinuria  $\geq$  1.0 g/day after the initial treatment for at least 4 weeks) NS and FSGS. Of the 41 cases of NS due to FSGS, 20 were new-onset. The device treatment was provided in conjunction with standard medications for FSGS/NS: steroids, cyclosporine A, or other immunosuppressive medications. Each patient received 3-12 treatments with the device.

Adverse events (safety) were not assessed.

In summary, among the 41 patients, encouraging two-year efficacy data were provided for 29 patients (assuming constant enrollment) and five-year data were available for 15 patients. This may be due to steady enrollment throughout the study period.

### Safety Assessment

The studies above did not report reliable adverse event data. However, the safety data from adults with functional hypercholesterolemia (FH) treated with the device can be extrapolated to safety for adults with FSGS treated with the LIPOSORBER® LA-15 System. The table below demonstrates the rates of various adverse events in adults with FH treated with the LIPOSORBER® LA-15 System:

Adverse Event	Episodes		Pa	ntients
Hypotension	41	0.8%	25	33.8%
Nausea/Vomiting	27	0.5%	14	18.9%
Flushing/Blotching	20	0.4%	9	12.2%
Angina/Chest pains	10	0.2%	8	10.8%
Fainting	9	0.2%	6	8.1%
Lightheadedness	7	0.1%	6	8.1%
Anemia	6	0.1%	6	8.1%
Abdominal discomfort	5	0.1%	3	4.1%
Numbness/Tingling	4	0.1%	4	5.4%
Tachycardia	4	0.1%	3	4.1%
Headache	3	0.1%	3	4.1%
Shortness of Breath	3	0.1%	2	2.7%
Hemolysis	3	0.1%	2	2.7%
Bradycardia	3	0.1%	2	2.7%
Itching/Hives	2	0.04%	2	2.7%
Blurred Vision	2	0.04%	2	1.4%

### 1.8.2 Pediatrics

Hattori et al. (2003) [13]: This study describes the outcomes of eleven (11) children with steroid resistant primary FSGS who were treated unsuccessfully with conventional-dose cyclosporine therapy and showed persistent nephrotic range proteinuria. At the time of treatment with the LIPOSORBER® LA-15 System, none of the patients had received a renal transplant ("pre-transplant"). At the start of the 7<sup>th</sup> apheresis treatment (average number of treatments: 11.5), prednisone was administered at a dose of 1mg/kg/d for 6 weeks, followed by a tapering schedule during subsequent months.

The effectiveness endpoint was the number of patients achieving remission of nephrotic syndrome. Other measures included renal function (i.e., GFR, degree of proteinuria, cholesterol level and complications of therapy.

The criteria used to assess clinical response were:

Remission of nephrotic syndrome (NS)

#### 1. INTRODUCTION

- Complete remission: reduction in urinary protein (< 4 mg/m²/h) for 3 consecutive days with normal serum albumin and cholesterol levels, and stable renal function
- Partial remission: lower urinary protein levels but persistent non-nephrotic proteinuria (protein< 40 mg/m²/h) with normal serum albumin</li>
- Renal Function (as GFR, in ml/min/1.73m<sup>2</sup>)
- Proteinuria (g/m²/day).

#### Results

#### Effectiveness:

- Achievement of remission (defined above) of nephrotic syndrome was observed in 7/11 patients (5 complete and 2 partial).
- Renal function (GFR) for the five (5) patients who achieved complete remission was normal during follow-up (median: 4.4 years, range: 4.0-11.1 years).
- Proteinuria declined in 7/11 patients (as evidenced by remission of nephrotic range proteinuria).

### Safety:

• Only one patient developed a complication (infection of the indwelling catheter used to receive the therapy).

#### Conclusion

The authors suggest that combined LDL-apheresis and prednisone therapy can be a valuable therapeutic option for treating patients with steroid resistant FSGS.

#### References

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### 1.9 Instructions for Use

Use of the LIPOSORBER® LA-15 System in adult and pediatric patients with FSGS is recommended to occur twice weekly for 3 weeks followed by once per week for six weeks.

### 1.9.1 Determining Plasma Volume to be Treated

The clinical experiences in Japan suggest that treating 60 mL/kg patient plasma volumes during a single procedure is acceptable for adult and pediatric patients with primary focal segmental glomerulosclerosis. The plasma volume to be treated can be calculated as follows:

STEP 1: Obtain patient weight (kilograms)

STEP 2: Multiply the patient weight by 60.

STEP 3: Round up the value from Step 2 to the nearest hundredth.

This is the plasma volume to be treated.

### **Example:**

STEP 1: Obtain patient weight.

Weight: 48kg

STEP 2: Multiply value from STEP 1 by  $60 \rightarrow 48 \times 60 = 2,880$ 

STEP 3: Round up value from STEP 2 to the nearest hundredth  $\rightarrow$  2,900 ml

This is the plasma volume to be treated.

The amount of plasma treated will require adjustment as clinically indicated by the physician in order to achieve and optimize individualized patient treatment goals.

### 1.9.2 Determining Heparin Dosage

Although heparin administration procedures vary and are adjusted to the requirements of the individual patient by a supervising physician, a proper heparinization schedule **must be** initiated before and maintained throughout LDL-apheresis to prevent clotting and subsequent blood path obstruction. The following are examples of heparinization schedules.

- 1. <u>Priming Solution</u>. Lactated Ringer's Injection, USP (1,000 ml) should contain 2,000-3,000 USP units of heparin.
- 2. <u>Loading Dose (Manual Infusion)</u>. Obtain PTT and PT pretreatment levels prior to initiation of LDL-apheresis therapy. If values are in the normal range, the recommended loading dose is approximately 25 USP units of heparin per kilogram of body weight. If a patient's PTT or PT is abnormally high, the physician should consider a lower loading dose of heparin.
- 3. Continuous Heparinization. Continuous heparinization is required during the LDL-apheresis procedure. Based upon a normal PTT and PT, approximately 25 USP units of heparin per kilogram of body weight per hour is recommended. During the first few apheresis treatments, coagulation test results should be monitored frequently to establish a coagulation profile for the individual patient. A monitoring schedule for these initial treatments should consist of a pre-heparinization PTT, PT, and activated clotting time (ACT) measurement. The ACT measurements should be performed at 30-minute intervals during the treatment. ACT levels should be maintained within a range of 180-250 seconds or 1.5 to 3 times the normal range. Once a patient's heparin regimen has been established, a patient's ACT may be followed less frequently during subsequent treatments.

A heparin pump is used to deliver heparin into the blood withdrawal line at a rate necessary to maintain a desired clotting time. A heparin pump infusion rate between 1,000-3,000 USP units of heparin per hour usually is sufficient.

Detailed Instructions for Use are set forth in the accompanying Operator's Manual for the LIPOSORBER® LA-15 System and in the instructions for use for the LIPOSORBER® LA-15 LDL Adsorption Column, SULFLUX® KP-05 Plasma Separator, and Tubing System for Plasmapheresis (NK-M3R(UL)). The procedures outlined in the Operator's Manual must be followed exactly as specified. No adjustments or modifications of such procedures not specifically stated in the Operator's Manual may be made. In the event of equipment or device failure or malfunction, discontinue the procedure and follow the instructions in the Operator's Manual.

## 1.10 Moving and Transportation of the MA-03

## **A**CAUTION

When moving the MA-03, do not put your feet close to the casters. They may get crushed.

### 1.10.1 Moving of the MA-03 Indoors

### Normal Moving

- Release the lock of casters.
- 2. After that, the MA-03 can be moved or turned freely.

## **A**CAUTION

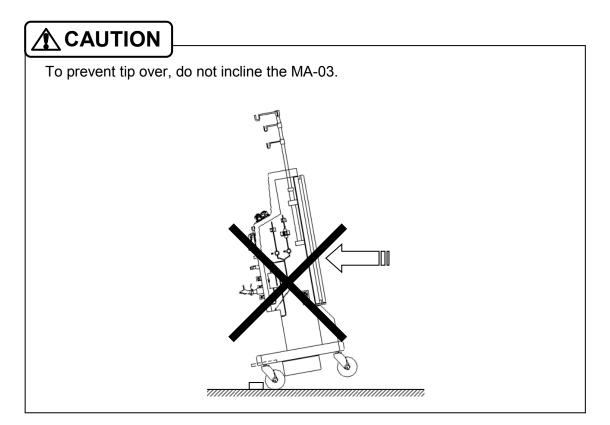
If moving the MA-03 down or up a slope (an angle over 10°), two people should be used.

# **⚠** CAUTION

When you move MA-03, please move the external lamp to the lowest position. And be careful not to hit the ceiling and the upper frame of the door.

### ■ Moving Over Different Floor Levels (i.e. Entrance of an elevator)

1. To prevent damage or falling of the machine, always move the machine slowly while rolling over different floor levels or small bumps.





Do not lift the machine by grasping the external lamp or bag hanger. This can damage the machine.

## 1.10.2 Transportation of the MA-03 Outdoors

- 1. The machine must not be moved across uneven surfaces (i.e., stone paved roads and the like).
- 2. If the machine needs to be moved across an uneven surface, protect it from vibration by placing the machine on a sturdy handcart with proper padding.
- 3. Before transporting the machine, remove all equipment and disposables such as solution bags, the external lamp and bag hangers.
- 4. "Power Failure" buzzer sounds if POWER ON Button was accidentally pressed while transporting the machine.



"Power Failure" buzzer stops when POWER OFF Button on the Operation Panel is pressed for more than 3 sec.

## 1.11 EMC information

The MA-03 conforms to the EMC standard of IEC60601-1-2:2001

## 1.11.1 Electromagnetic Emission and Electromagnetic Immunity

The MA-03 is intended for use in the electromagnetic environment specified below. The customer or the user of the MA-03 should assure that it is used in such an environment.

Emissions test	Compliance	Electromagnetic environment - guidance
RF emissions	Group 1	The MA-03 uses RF energy only for its internal
CISPR 11		function. Therefore, its RF emissions are very low and
		are not likely to cause any interference in nearby
		electronic equipment.
RF emissions	Class A	The MA-03 is suitable for use in all establishments
CISPR 11		other than domestic and those directly connected to the
Harmonic emissions	Class A	public low-voltage power supply network that supplies
IEC 61000-3-2		buildings used for domestic purposes.
Voltage fluctuations	Complies	
/ flicker emissions		
IEC 61000-3-3		

Guidance – electromagnetic immunity						
Immunity test	IEC60601 test level	Compliance level	Electromagnetic environment - guidance			
Electrostatic discharge (ESD) IEC 61000-4-2	±6kV contact ±8kV Air	±8kV Air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30 %.			
Electrical fast transient / burst IEC 61000-4-4	±2kV for Power supply line ±1kV for input / output line	±2kV for Power supply line ±1kV for input / output line	Mains power quality should be that of a typical commercial or hospital environment.			
Surge IEC 61000-4-5	±1kV differential mode ±2kV common mode	±1kV differential mode ±2kV common mode	Mains power quality should be that of a typical commercial or hospital environment.			
Voltage dips, short interruptions and voltage variations on power supply input lines IEC 61000-4-11	<5% Ut (>95% dip in Ut) for 0.5 cycle  40% Ut (60% dip in Ut) for 5 cycle  70% Ut (30% dip in Ut) for 25 cycle  <5% Ut (>95% dip in Ut) for 5 s	5% <i>Ut</i> (>95% dip in <i>Ut</i> ) for 0.5 cycle  40% <i>Ut</i> (60% dip in <i>Ut</i> ) for 5 cycle  70% <i>Ut</i> (30% dip in <i>Ut</i> ) for 25 cycle  <5% <i>Ut</i> (>95% dip in <i>Ut</i> ) for 5 s	Mains power quality should be that of a typical commercial or hospital environment. If the user of the MA-03 requires continued operation during power mains interruptions, it is recommended that the MA-03 be powered from an uninterruptible power supply or a battery.			
Power frequency (50/60Hz) magnetic field IEC61000-4-8	3A/m	3A/m	Power frequency magnetic field should be measured in the intended installation location to assure that it is sufficiently low.			
NOTE Ut is the a.c. mains voltage prior to application of the test level.						

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Guidance – electromagnetic immunity						
Immunity test	IEC60601	Compliance	Electromagnetic environment - guidance			
	test level	level				
			Potable and mobile RF communications equipment should be used no closer to any part of the MA-03 including cables, than the recommended separation to the frequency of the transmitter.			
Conducted RF	3Vrms	3Vrms	Recommended separation distance			
IEC61000-4-6	(150kHz		<i>d</i> =1.2√ <i>P</i>			
	to		<i>d</i> =1.2√ <i>P</i> (80MHz to 800MHz)			
	80MHz)		$d=2.3\sqrt{P}$ (800MHz to 2.5GHz)			
Radiated RF						
IEC61000-4-3	3V/m (80MHz to 2.5GHz)	3V/m	where $P$ is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacture and $d$ is the recommended separation distance in meters (m) ( $\sqrt{P}$ is a square root of P.) Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey,"a" should be less than the compliance level in each frequency range."b"  Iterference may occur in the vicinity equipment maked with the following symbol:			

NOTE 1 At 80MHz and 800MHz, the higher frequency range applies.

NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.

"a" Field strengths from fixed transmitters, such as base stations for radio (cellular / cordless) telephones and land mobile ratios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered If the measured filed strength in the location in which the MA-03 is used exceeds the applicable RF compliance level above, the MA-03 should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as re-orienting or relocating the MA-03.

"b" Over the frequency range 150kHz to 80MHz, it is preferable that the field strengths should be less than 3 V/m.

# 1.11.2 Recommended separation distances between portable and mobile RF communications equipment and the MA-03

The MA-03 is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or the user of the MA-03 can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the MA-03 as recommended below, according to the maximum output power of the communications equipment.

Rated	Separation distance according to frequency of transmitter					
maximum		m				
output power	150kHz to 80MHz	80MHz to 800MHz	800MHz to 2.5GHz			
of transmitter	<i>d</i> =1.2√ <i>P</i>	<i>d</i> =1.2√ <i>P</i>	<i>d</i> =2.3√ <i>P</i>			
W						
0.01	0.12	0.12	0.23			
0.1	0.38	0.38	0.73			
1	1.2	1.2	2.3			
10	3.8	3.8	7.3			
100	12	12	23			

For transmitters rated at a maximum output power listed above, the recommended separation distance *d* in meters (m) can be estimated using the equation applicable to the frequency of the transmitter, where *P* is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.

NOTE 1 At 80MHz and 800MHz, the separation distance for higher frequency range applies.

NOTE 2 These guidelines may no apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.

## 1.12 The MA-03 Danger, Warning and Caution

# **⚠** DANGER

Do not use the machine where highly flammable anesthetic or flammable gas is used, in a high pressure oxygen room or in oxygen tent.

This could trigger an explosion.

## **⚠** WARNING

Use of Machine by an unqualified operator may result in injury or death to the patient and the operator, or damage to the MA-03.

# **MARNING**

Grounding reliability can only be achieved when the machine is connected to an equivalent receptacle marked "Hospital only" or "Hospital grade".

Never use any adaptor which breaks the contact between the machine ground and the receptacle ground.

When not grounded, this could cause electric shock.

# **MARNING**

In the machine's vicinity, never use devices that cause electromagnetic interference, such as mobile phones, CB wireless transmitters, electric cauteries or defibrillators while the machine is in operation. The machine may malfunction.

# **⚠** WARNING

If any device which transmits electromagnetic wave is used around the MA-03, this may cause the MA-03 to malfunction.

Please follow instructions indicated in section 1.11 of this manual.

## **MARNING**

Use only authorized accessories for the machine.

If an improper accessory is connected to the MA-03, physical injury may result.

## **MARNING**

The machine can not be used if a defibrillator needs to be used on the patient.

Do not touch the machine when discharging the defibrillator.

Confirm proper operation of the machine after defibrillator use. Use of a defibrillator could negatively affect the machine's safe operation.

# **MARNING**

Only use specified power supply voltage otherwise fire or electric shock may occur.

## **MARNING**

Do not open access covers of the MA-03.

This could cause fire or electric shock.

# **MARNING**

Do not place heavy apparatus on the power cord.

This could cause fire or electric shock.

## **A** WARNING

A new, sterile transducer protective filters should be attached to all pressure ports.

This will prevent cross infection to patients through the machine.

If the transducer protective filters are wet and air is not able to pass, replace the transducer protective filter with a new one and clear the monitor line.

## **MARNING**

If the external transducer protective filter, internal transducer protective filter and the internal transducer are contaminated with blood replace the filter with a new one and sterilize or replace the transducer and the associated parts.

Only authorized KANEKA PHARMA AMERICA LLC service personnel should perform any parts replacement or sterilization.

## **WARNING**

Pressure changes resulting from line separation or needle removal may be too subtle for the system to detect.

All connections must be properly secured and visually confirmed regularly.

Access sites and connections should remain uncovered for monitoring.

# **A** WARNING

Instructions for operation:

- 1. The operator must confirm and verify that the indicated value is equal to the entered value every time the operator sets a parameter.
- 2. If the indicated value is not equal to the entered value, treatment must not be started in any case.

## **MARNING**

Make sure fluid is not poured or splashed on the machine.

# **A** WARNING

Maintenance:

Only authorized KANEKA PHARMA AMERICA LLC service personnel should perform assembly, installation, adjustment, or repair of the machine.

# **A** CAUTION

The machine should be installed in the following locations:

- 1. Level and stable location.
- 2. A location with three (3) feet of space around the machine to let air circulate.
- 3. Ambient temperature should be between 50-95 degrees Fahrenheit and the humidity should be less than 85%.
- 4. A location for properly grounding the machine.

# **⚠** CAUTION

The machine should not be installed in the following locations:

- A location where the machine is exposed directory to the sunlight for a long time.
   Especially, the LCD in the machine will be deteriorated by the ultraviolet ray of the sunlight. Therefore, do not leave the machine under direct sunlight for a long time.
- 2. A location where the machine is affected by splashed water or steam.
- 3. A location affected by vibrations and shocks.
- 4. A location where there is flammable or corrosive gases and fire.
- 5. A location where chemicals are stored.

## **A** CAUTION

If there is dew condensation on the machine, dry it well before turning the electric power on. Electric shocks could occur.

## **⚠** CAUTION

While in use, constantly monitor the machine for safe and proper usage.

## **A** CAUTION

Do not use ballpoint pens or other sharp-pointed objects to push the switches (buttons and keys). This may damage the front panel.

## **⚠** CAUTION

Be sure to handle electric plugs properly, or electric shocks and fire may occur:

- 1. Never handle electric plugs with wet hands.
- 2. When pulling electric plugs, do not pull the cord.
- 3. If the machine will not be used for a long time, unplug the power cord.

## **⚠** CAUTION

When cleaning the machine, do not use solvents like thinner and benzene and the like. The machine's surface may become damaged.

## **CAUTION**

Set the bag hangers lower than six (6) feet of height to minimize the risk of the machine tilting over.



Measure for LCD's abnormality

If the LCD screen does not display any contents or a key has no response, turn off the machine immediately and then perform blood return by using the manual pump handle. (Please refer to Chapter 7.6 Manual Blood Return of the operator's manual )

[Operating keys in abnormal state of the LCD screen may lead to an unintended action of the machine.]



Do not leave the machine near the ultraviolet-rays sterilization light for a long time. [Ultraviolet-rays causes a deterioration or discoloration of the plastic parts on the outer surface and the LCD, and that causes a malfunction of the machine.]

### **Side Panel Caution Label**

A caution label is located at the position shown in Figure 1.1. Before operating the MA-03, read the label.

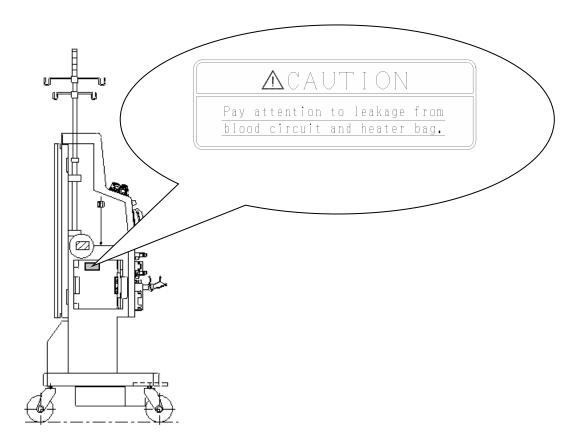


Figure 1.1 Caution Label

## 1.13 Limits to the Manufacturer's Responsibility

- The LIPOSORBER® LA-15 System must be used in accordance with this Operator's Manual. The use of operating or maintenance procedures other than those published by Kaneka Pharma America LLC or the use of disposable device components not recommended by Kaneka Pharma America LLC may result in injury or loss of life. Kaneka Pharma America LLC, the manufacturers of the MA-03 or the disposable device components, or any distributor of the LIPOSORBER® LA-15 System will not be responsible for resulting injury or damage if the procedures to operate and maintain the LIPOSORBER® LA-15 System are other than those specified in the instructions for use provided for each of the disposables and this Operator's Manual. Persons performing the procedures must be appropriately trained and qualified.
- In no event shall Kaneka Pharma America LLC or the manufacturers of the MA-03 or of the disposable device components or any distributor of the LIPOSORBER® LA-15 System be liable for any losses or damages caused or resulting from any negligence in the selection of patients outside the indicated population, operation of the LIPOSORBER® LA-15 System, or treatment of patients with the LIPOSORBER® LA-15 System by any third party.
- Except as expressly set forth herein, Kaneka Pharma America LLC makes no warranty whatsoever, express or implied, and specifically disclaims any warranty of merchantability or fitness for a particular purpose as to the LIPOSORBER® LA-15 System.
- Certain solutions and disposable products available from other manufacturers are used with the LIPOSORBER® LA-15 System. Kaneka Pharma America LLC has no control over variability, tolerances, mechanical strength or changes in these products which may exist from time to time. Therefore, Kaneka Pharma America LLC cannot ensure that the disposable products of other manufacturers will function in a satisfactory manner and expressly disclaims any responsibility or liability for any injury, harm, damages or loss resulting from the use or malfunction of such products.

#### 1. INTRODUCTION

## 2. OVERVIEW OF THE MA-03

### 2.1 Environmental Conditions

#### ■ Safe Operating Conditions

Ambient temperature 15 to 35°C

Relative humidity 30 to 85% (Non condensing)

Air pressure 700 to 1060hPa (0.66 to 1.0 atmospheres)

#### ■ Safe Storage and Transportation Conditions

Ambient temperature -20 to 60°C

Relative humidity 10 to 95% (Non condensing)

## **A**CAUTION

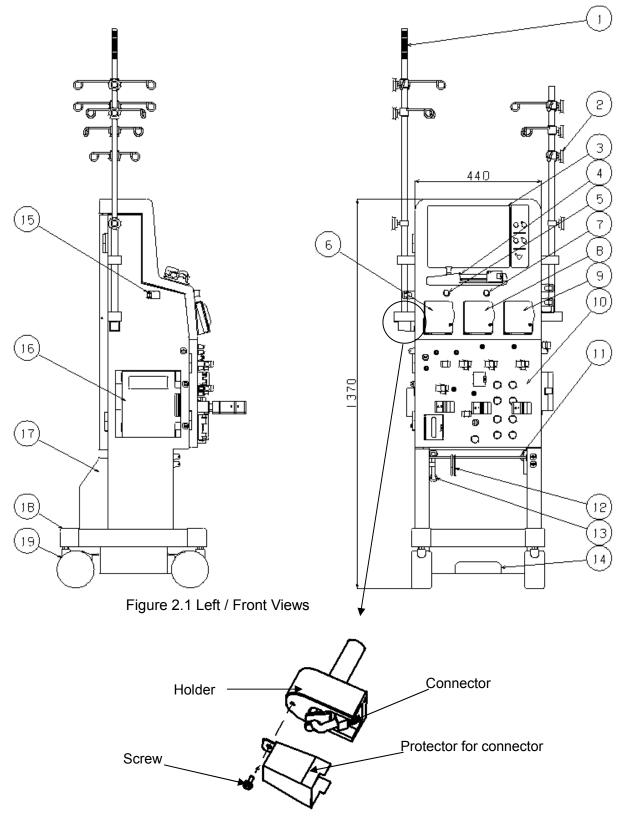
Particular attention should be given when storing the MA-03 for more than 15 weeks or when transporting.

#### ■ Electric Power Supply (Electric Facility)

Nominal voltage	Frequency	Current
115V AC	50/60Hz	5A

## 2.2 Configurations of the MA-03

## 2.2.1 Appearance

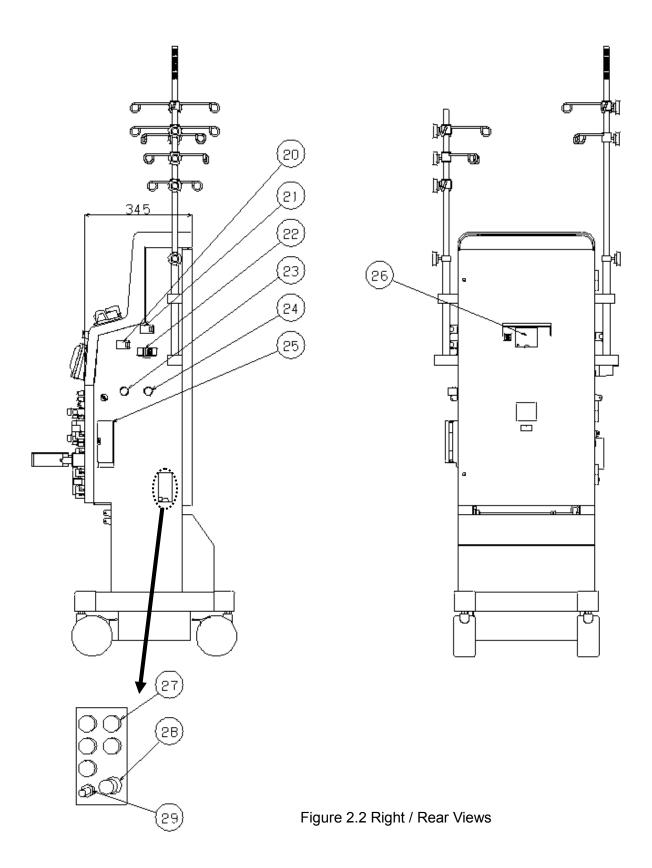


- 1. External Lamp
- 2. Bag Hanger
- 3. Monitor/Operation Panel (see "Monitor/Operation Panel" in Section 2.3.2.)
- 4. Infusion Pump (IP) (see "Infusion Pump" in Section 2.3.5.)
- 5. Blood Flow Rate Turning Knob
- 6. Blood Pump (BP) (see "Blood Pump, Plasma Pump and Replacement Fluid Pump" in Section 2.3.4.)
- 7. Plasma/Replacement Fluid Flow Rate Turning Knob
- 8. Plasma Pump (PP) (see "Blood Pump, Plasma Pump and Replacement Fluid Pump" in Section 2.3.4.)
- 9. Replacement Fluid Pump (RP) (see "Blood Pump, Plasma Pump and Replacement Fluid Pump" in Section 2.3.4.)
- 10. Front Panel (see "Front Panel" in Section 2.3.3.)
- 11. Power Cord
- 12. Hook for Waste Bag
- 13. Manual Pump Handle
- 14. Waste Fluid Container Table
- 15. Fluid Detector 1 (FD1)
- 16. Blood Warmer (Plate Heater; PH)
- 17. Box for the Operator's Manual
- 18. Rubber cap
- 19. Caster



Procedure to detach the external lamp (with bag hanger):

- Remove connector protector and disconnect connector. Protector is held by a screw.
- Loosen pole screw and lift pole upward.



- 20. Fluid Detector 2 (FD2)
- 21. Fluid Detector 3 (FD3)
- 22. Drip Detector (DD)
- 23. Replacement Fluid Valve (V1)
- 24. Regeneration Fluid Valve (V2)
- 25. Conductivity Detector (CD)
- 26. Data logging unit
- 27. Fuses
- 28. System-Start Switch
- 29. Connection Terminal for Potential Equalization Conductor



#### System-Start Switch:

If the built-in battery is completely discharged and the MA-03 will not power on after pressing the POWER ON button, press this switch.

#### Connection Terminal for Potential Equalization Conductor:

The connection terminal for potential equalization conductor is the terminal which connects to the potential equalization bus-bar from the electrical installation.

#### 2.2.2 Monitor/Operation Panel

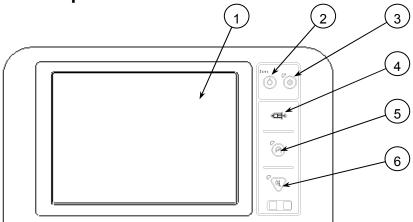


Figure 2.3 Monitor/Operation Panel

#### 1. LCD

Contents displayed on the LCD vary depending on the selected process, and the status of the alarm function. By touching keys on the LCD the MA-03 can be operated and conditions are set.



Operation of the MA-03 and setting of certain operating conditions can be managed on the LCD where information, instructions and alarm status are shown with text or graphics.

#### 2. POWER OFF Button

When this button is continually pressed for 3 seconds or longer, the MA-03 powers OFF.

#### 3. POWER ON Button with Operating Lamp

Press this button to power ON the MA-03. The operating lamp lights while the MA-03 is ON.

#### 4. INFUSION PUMP Indicator

The indicator lights or flashes while the Infusion Pump is operating.

#### 5. BLOOD PUMP Button and Indicator

This button is only active and the indicator lamp is lit in the processes of Rinsing, Priming, Treatment and Return. When this button is pressed while active, the machine enters into "Process Suspended" status, and all pumps stop and all valves close. The indicator lamp blinks and the "Process is suspended" screen appears on the LCD. To resume the process, press this button again.

#### 6. MUTE Button and Indicator

While the alarm buzzer is sounding, press this button to mute the buzzer for up to 2 minutes. If another alarm-triggering event occurs during that period, the alarm buzzer sounds again. The indicator flashes while the alarm buzzer is muted.

## **A** CAUTION

While an "Alarm" condition exists, the "Process is suspended" screen is replaced with the "Alarm" screen. The "Process is suspended" screen will appear when all alarm conditions are resolved.

## 2.2.3 Front Panel

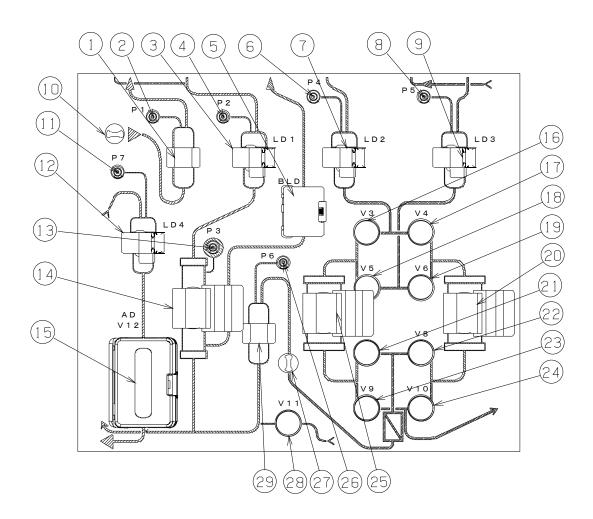
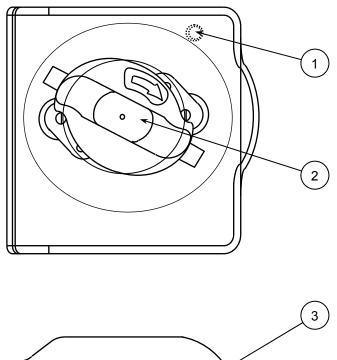


Figure 2.4 Front Panel

- 1. Arterial Chamber Holder
- 2. Arterial Pressure Port (P1)
- 3. Blood Inlet Level Detector (LD1)
- 4. Blood Inlet Pressure Port (P2)
- 5. Blood Leak Detector (BLD)
- 6. Plasma Inlet Pressure Port (P4)
- 7. Plasma Inlet Level Detector (LD2)
- 8. Replacement Fluid Pressure Port (P5)
- 9. Replacement Fluid Level Detector (LD3)
- 10. Arterial tube holder
- 11. Venous Pressure Port (P7)
- 12. Venous Level Detector (LD4)
- 13. Plasma Pressure Port (P3)
- 14. Plasma Separator Holder
- 15. Air Detector (AD), Venous Valve (V12), and Blood/Saline Detector (BSD)
- 16. Plasma Inlet Left Valve (V3)
- 17. Plasma Inlet Right Valve (V4)
- 18. Replacement Fluid Left Valve (V5)
- 19. Replacement Fluid Right Valve (V6)
- 20. Adsorption Column Right Holder
- 21. Plasma Outlet Left Valve (V7)
- 22. Plasma Outlet Right Valve (V8)
- 23. Waste Fluid Left Valve (V9)
- 24. Waste Fluid Right Valve (V10)
- 25. Adsorption Column Left Holder
- 26. Plasma Outlet Pressure Port (P6)
- 27. Plasma Outlet tube Holder
- 28. Rinse Valve (V11)
- 29. Plasma outlet chamber holder

## 2.2.4 Blood Pump, Plasma Pump, and Replacement Fluid Pump



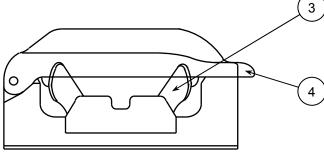


Figure 2.5 Blood Pump, Plasma Pump, and Replacement Fluid Pump

1. Sensor

The sensor detects whether the pump cover is open or closed.

- 2. Rotor
- 3. Tube Clamp

The tube clamp fastens the pump segment.

4. Pump Cover

## 2.2.5 Infusion Pump

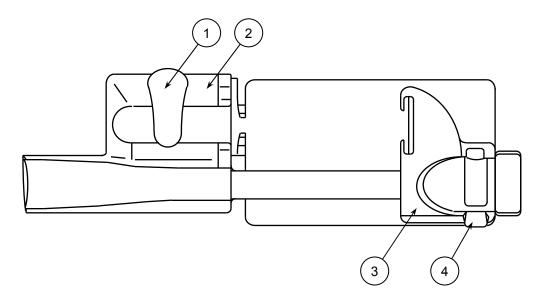


Figure 2.6 Infusion Pump

#### 1. Holder Lever

The holder lever secures the syringe.

#### 2. Holder

The flange of the syringe cylinder is set into the holder.

#### 3. Syringe Slider

The slider moves the syringe plunger.

#### 4. Unlock Button

While the unlock button is pressed, the syringe slider becomes unlocked and can be moved freely.

## 2.3 Specifications

### 2.3.1 Dimensions and Weight

Dimensions

 Height
 137cm (54.0 inches)

 Width
 44cm (17.3 inches)

 Depth
 34.5cm (13.6 inches)

Floor Space Approximately 47cm (18.5 inches) wide by 59cm

(23.2 inches) deep

■ Weight

Standard system Approximately 77kg (170 lbs.)

# 2.3.2 Electric Safety (Classified According to EN / IEC60601-1)

■ Type of protection against electric shock Class I equipment

Degree of protection against electric shock

Type B Applied part Symbol:



Degree of protection against the ingress of water

Drip proof Symbol: **IPX1** 

■ Degree of safety of application in the presence of a flammable anesthetic mixture with air or with oxygen or nitrous oxide

Not suitable for use

■ Mode of operation

Continuous operation

Type Label

#### APHERESIS MACHINE

MODEL : KANEKA MA-03 POWER : 115V~ 50/60Hz 350VA









Distributor

KANEKA Pharma America LLC 546 Fifth Avenue, 21st Floor New York, NY 10036 USA

Manufacturer

NIKKISO CO.,LTD.

20-3, Ebisu 4-Chome, Shibuya-ku, Tokyo 150-6022, Japan 2006-04

SN 66001-01

#### 2.3.3 Power Supply

#### ■ Voltage

115 V AC 115 V AC  $\pm$ 10 %, 50/60 Hz  $\pm$ 1 Hz

## **MARNING**

Grounding reliability can only be ensured when the machine is connected to an outlet marked "Hospital only" or "Hospital grade".

Never use any adaptor which bypasses the machine ground and the receptacle ground.

Improper or no grounding may cause electric shock.

#### **■** Power Consumption (Maximum)

350 VA 5 A

#### Battery

Kind Nickel-metal hydride battery (Ni-MH)

Capacity 24 V/1.9 Ah

Storage - Charging of built-in battery

Charge the battery every 6 months in the following procedures,

- 1. Connect the power plug of the machine to the electric outlet.
- 2. Stay the machine power-on for 48 hours.

## NOTICE

If the battery has been completely discharged, the machine cannot be turned on by pressing the POWER ON button in the operation panel.

Then turn the machine on by pushing System-Start Switch in the power supply unit in the right side panel.

## 2.3.4 Fuses (Power Unit)

Nominal voltage	Power line	Heater line	Battery line
115 V AC	F1, T5AH250V	F3, T2AH250V	F5, T1AH250V
	F2, T5AH250V		

F4, Unused

#### 2.3.5 Monitoring Parts



The setting values marked "\*" are user changeable.

The alarm range of setting values are shown between parentheses and the lower limit cannot exceed the higher limit.

Limit value is set by every facility.

Variable range is shown between parentheses.

#### **■** Arterial Pressure

Measurement range —300 to +300 mmHg

Measurement accuracy  $\pm 10 \text{ mmHg}$ 

Fixed alarm points Upper limit +200 mmHg\* (0 to +300 mmHg)

Lower limit -170 mmHg\* (-250 to 0 mmHg)

Alarm delay time Maximum 2 seconds

#### **■** Blood Inlet Pressure

Measurement range —200 to +600 mmHg

Measurement accuracy  $\pm 10 \text{ mmHg}$ 

#### **■** Plasma Pressure

Measurement range −200 to +600 mmHg

Measurement accuracy ±10 mmHg

#### ■ Plasma Inlet Pressure

Measurement range —200 to +600 mmHg

Measurement accuracy ±10 mmHg

#### **■** Plasma Outlet Pressure

Measurement range —200 to +600 mmHg

Measurement accuracy  $\pm 10 \text{ mmHg}$ 

#### ■ Replacement Fluid Pressure

Measurement range —200 to +600 mmHg

Measurement accuracy ±10 mmHg

#### **Venous Pressure**

Measurement range -200 to +600 mmHg

Measurement accuracy ±10 mmHg

Auto set alarm range Upper limit +60 mmHg\* (0 to +100 mmHg)

Lower limit -40 mmHg\* (-100 to 0 mmHg)Upper limit +170 mmHg\* (0 to +300 mmHg)

Fixed alarm points (-200 + 100 mmHg)

Lower limit -50 mmHa\*

Alarm delay time Maximum 2 seconds

#### Plasma Separator Differential Pressure

-300 to +500 mmHg Measurement range

Measurement accuracy ±10 mmHg

Upper limit +100 mmHg\* Fixed alarm points (0 to Limit value mmHg)

> Lower limit -50 mmHg\* (-150 to 0 mmHg)

Maximum 2 seconds Alarm delay time

#### **TMP**

Measurement range -100 to +500 mmHg

±10 mmHg Measurement accuracy

Fixed alarm points Upper limit +60 mmHg\* (0 to Limit value mmHg)

> Lower limit -50 mmHg\* (-150 to 0 mmHg)

Maximum 2 seconds Alarm delay time



Definition

 $TMP = \left(\frac{P2 + P6}{2}\right) - P3$ P2 = Blood inlet pressure P3 = Plasma pressure

P6 = Plasma outlet pressure (=Blood outlet pressure)

#### **Adsorption Column Differential Pressure**

-300 to +500 mmHg Measurement range

Measurement accuracy ±10 mmHg

Fixed alarm points Upper limit +120 mmHg\* (0 to Limit value mmHg)

> Lower limit \_60 mmHg\* (-150 to 0 mmHg)

Maximum 2 seconds Alarm delay time

#### Blood/Saline Detector (Air detector block)

Method Optical

Judge Blood or No blood

#### Air Detector

Method Ultrasonic waves Sensitivity 0.02 mL (bubble)

Blood flow rate: 200 mL/min

0.0003 mL (micro bubble: blood/air mixture)

Blood flow rate: 200 mL/min

#### **■** Blood Leak Detector

Method Optical

Sensitivity 0.25 mL blood/min Hematocrit 32 %

(Standard plasma flow rate: 50 mL/min) 0.4 mL blood/min Hematocrit 32 % (Maximum plasma flow rate: 90 mL/min)

Percentage terms displayed as blood leak data shows approx. 2% attenuation out of 1mL leak while standard

(100%) means no blood leak.

Alarm response Response from the blood leak detector delays to remove

disturbances.

The delayed response depends on the plasma flow rate.

#### **■** Fluid Detector

Method Ultrasonic waves Sensitivity 0.5 mL (bubble)

Fluid flow rate: 200 mL/min

Alarm delay time 2 seconds at a maximum

#### ■ Level Detector

Method Ultrasonic waves

Sensitivity  $\pm 1.0 \text{ mm}$ 

Alarm delay time 2 seconds at a maximum

#### ■ Conductivity Detector

Measurement range 0 to 80 mS/cm

Measurement accuracy ±30 % (Temperature of liquid: 15 to 35 °C)
Alarm points ±30 % (Temperature of liquid: 15 to 35 °C)
Lower conductivity (Regeneration solution)

42.0 mS/cm

Lower conductivity (Replacement solution)

11.2 mS/cm

Upper conductivity (Replacement solution)

20.8 mS/cm

Alarm delay time 2 seconds at a maximum

#### 2.3.6 Actuators

#### ■ Blood Pump

I.D. 4.0mm O.D 8.0mm Tubing size Setting range 0, 7 to 200 mL/min

Flow rate accuracy Set value  $\pm 5$  % ( $\pm 10$  %, with the following conditions)

Minimum –100 mmHg(-150 mmHg) Inflow pressure

Maximum –30 mmHg(+150mmHg) Minimum +100 mmHg (0 mmHg)

Outlet pressure Maximum +200 mmHg (+500mmHg)

Stoppage of the Blood Pump is automatically

Protection system

monitored.

Rotation (reverse rotation) of the Blood Pump is

automatically monitored.

Blood flow rate = Rotation of the Blood Pump Display method

#### Plasma Pump

Outlet pressure

In case of using as the Plasma Pump

Tubing size I.D. 2.7mm O.D 6.7mm Setting range 0. 4 to 90 mL/min

Flow rate accuracy Set value  $\pm 5$  % (  $\pm 10$  %, with the following conditions)

Minimum 0 mmHg(-150 mmHg) Inflow pressure

Maximum +200 mmHg(+250mmHg) Minimum +130 mmHg (0 mmHg) Maximum +240 mmHg (+500mmHg)

Protection system Stoppage of the Plasma Pump is automatically.

Rotation (reverse rotation) of the Plasma Pump is

automatically monitored.

Plasma flow rate = Rotation of the Plasma Pump Display method

#### Replacement Fluid Pump

When PA2 is selected

I.D. 2.7mm O.D 6.7mm Tubing size

Setting range 0, 4 to 90 mL/min

Flow rate accuracy Set value  $\pm 5$  % (  $\pm 10$  %, with the following conditions)

Minimum 0 mmHg Inflow pressure Maximum +80 mmHg

Minimum 0 mmHg (-50 mmHg)

Outlet pressure Maximum +50 mmHg (+500mmHg)

Protection system Stoppage of the Replacement Fluid Pump is

automatically monitored.

Rotation (reverse rotation) of the Replacement Fluid

Pump is automatically monitored.

Display method Replacement fluid flow rate = Rotation of the

Replacement Fluid Pump

#### ■ Infusion Pump

Setting range 0.0 to 10.0 mL/h
Outlet rate accuracy 7 % of setting value

Back pressure +500 mmHg

Type of syringe 20 mL disposable syringe (luer lock)

Bolus process 1500 mL/h Total flow measurement range 0 to 99.9 mL

Total flow measurement accuracy ±10 %

Protection system Stoppage of the Infusion Pump is automatically

monitored.

Reverse movement of the Infusion Pump is

automatically monitored.

#### ■ Blood Warmer

Setting range 35.0 to 39.0 °C Measurement range 10.0 to 50.0 °C

Measurement accuracy Measurement value ±0.8 °C

Blood flow rate: 100mL/min, at a constant ambient

temperature

Alarm point Upper limit 41 °C

## 2.4 Disposable Parts

## **⚠** CAUTION

- 1. Only use disposable parts that are approved.
- 2. Disposables (blood tube sets, plasma separators, syringes, etc.) are to be disposed of according to the applicable laws and regulations.

#### Use following disposable parts.



Disposables should be used in accordance with the instructions provided in the Instruction for Use of each device.

### 2.4.1 Adsorption Column

#### PA2

• LIPOSORBER® LA-15

## **⚠** CAUTION

The method for Rinsing, Priming and/or Treatment depends on the model/type of the disposables. Confirm that each product can be applicable to the machine by consulting the Instruction for Use of each device.

### 2.4.2 Blood Tubing

Tubing System for Plasmapheresis (NK-M3R(UL))

## 2.4.3 Plasma Separator

SULFLUX® KP-05 Plasma Separator

## 2.4.4 Syringe for Infusion Pump

20mL Syringe (luer lock)



Only use a 20mL luer lock listed above. Use of unapproved syringes may cause inaccurate heparin infusion.

### 2.5 Environmental Issues



Properly dispose of all disposables and other device components according to facility and local governing ordinances.

The MA-03 contains the following materials listed below.

#### Metals

- Stainless steel
- Aluminum
- Copper
- Iron
- Brass

#### Plastics

- Polycarbonate (PC)
- Polysulfone (PSU)
- Polyamide (PA)
- Polyoxymethylene (POM)
- Polyvinyl Chloride (PVC)
- Polyurethane Rubber (PUR)
- Monomer-Cast Nylon (UMC)
- Acrylonitrile-Butadiene-Styrene (ABS)
- Acrylonitrile-Styrene-Acrylate (ASA)

#### Other Materials

- Electronic components, such as LCD and P.C.B.
- Glass, Ceramic
- Nickel-Metal Hydride Battery (Ni-MH battery)

#### 2. OVERVIEW

## 3. TREATMENT METHOD OF THE MA-03

## 3.1 Applicable Treatment

The MA-03 is applicable for LDL-C plasma adsorption treatment.

#### ■ Plasma Adsorption Treatment

The blood withdrawn from the patient is separated into plasma and blood cells by passing through the membrane type plasma separator. Plasma is led to the adsorption column where specific substances are adsorbed and removed.



## 3.2 Plasma Adsorption Treatment

#### 3.2.1 Overview of PA2

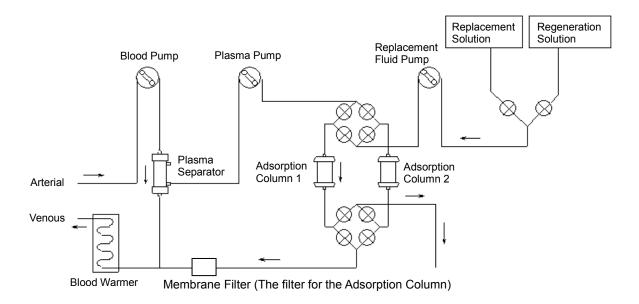


Figure 3.1 PA2

- 1. The blood which is withdrawn by the Blood Pump passes the Plasma Separator, and that is separated into blood cells and plasma.
- 2. Passing the Adsorption Column 1 where specific substance is adsorbed and removed, plasma joins the blood cells and return to the patient via Venous Access.
- 3. After the preset volume of plasma is processed in the Adsorption Column 1, the path of plasma is automatically switched to the Adsorption Column 2.
- 4. While plasma is processed in the Adsorption Column 2, the Adsorption Column 1 is regenerated.
- 5. Thus the two adsorption columns repeat adsorption and regeneration, to keep treatment until target volume of plasma is processed.



#### Regeneration:

The specific substance is flushed with the exclusive regeneration fluid from the adsorption column. Regeneration fluid is replaced with replacement fluid and the column is recovered to the usable state.

## 3.2.2 Action of PA2

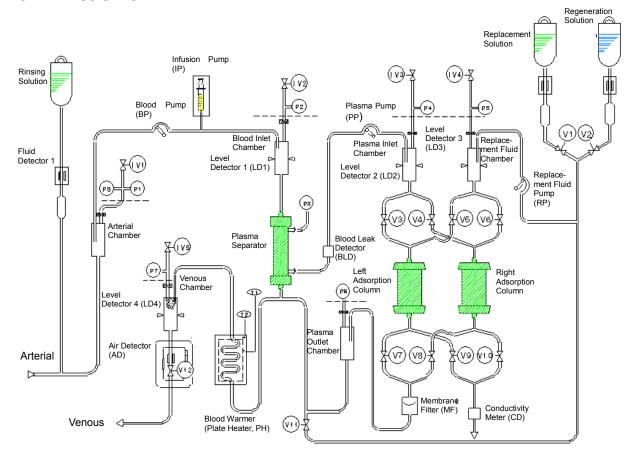
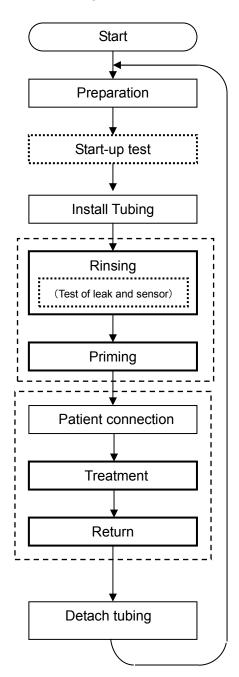


Figure 3.2 PA2

- (1) Blood is withdrawn from the patient by the Blood Pump (BP) through the Arterial Chamber. The withdrawn blood is led to the Plasma Separator through Blood Inlet Chamber with-anticoagulant which is infused by the Infusion Pump (IP).
- (2) The blood in the Plasma Separator is separated into blood cells and plasma, and plasma is led to the Left Adsorption Column by the Plasma Pump (PP) through the Blood Leak Detector (BLD) and the Plasma Inlet Chamber.
- (3) The specific substance contained in plasma is adsorbed in the Left Adsorption Column and removed. Plasma is led to the Membrane Filter (MF) and the Plasma Outlet Chamber, and mixed with the blood cells, which has been separated by the Plasma Separator.
- (4) The mixed blood is warmed up to proper temperature in the Blood Warmer (PH), and is returned to the patient through the Venous Chamber and the Air Detector (AD).
- (5) After the preset volume of plasma is processed in the Left Adsorption Column, the flow path of plasma is changed by the Plasma Inlet Left Valve (V3), the Plasma Inlet Right Valve (V4) and the Plasma Outlet Left Valve (V7), and the Plasma Outlet Right Valve (V8). Plasma is led to the Right Adsorption Column, and the adsorption process continues.
- (6) While plasma is processed in the Right Column, plasma in the Left Column is flushed out with Replacement Fluid, which is led to the column by the Replacement Fluid Pump (RP). The flow path is changed by the Replacement Fluid Valve (V1) and the Regeneration Fluid Valve (V2) to lead regeneration fluid, with which the specific substance is flushed out. And the Adsorption Column recovers to usable state. Then, the flow path is changed again by the Replacement Fluid Valve (V1) and the Regeneration Fluid Valve (V2) to lead Replacement Fluid, with which Regeneration Fluid is Replaced. This series of process is called regeneration process.
- (7) After the preset quantity of plasma in the Right Adsorption Column is processed, the flow path is changed by the plasma Inlet Left Valve (V3), the Plasma Inlet Right Valve (V4) and the Plasma Outlet Left Valve (V7), and the Plasma Outlet Right Valve (V8), plasma is led to the Left Adsorption Column where the adsorption process continues.
- (8) As mentioned above, each Adsorption Column alternates adsorption and regeneration process, and performs treatment.

## 3.3 Operation Flow

Here is the general flow of operation.



Check all disposables necessary for the procedure and collect them.

The safety functions of the MA-03 are checked before the treatment starts.

Install the tubing and disposables to the MA-03.

The tubing and disposables are rinsed with rinsing solution.

(Safety function of the machine, leak of the tube etc. are confirmed before the treatment starts.)

The tubing system and disposables are primed with heparinized priming solution.

Patient is connected to the extracorporeal circuit through the arterial and venous lines.

Apheresis is performed.

Arterial line is disconnected from the patient and connected to Return solution.

Blood and plasma in the extracorporeal circuit are returned to the patient.

The tubing system and disposables are removed from the MA-03 and properly discarded.

Figure 3.3 Operation Flow (Conceptual Diagram)



Once the current process step completes, the step of the machine can be forwarded to the next process, and can not return to the previous process step.

#### 3. TREATMENT METHOD

## 4. DISPLAY SCREEN OF THE MA-03

### 4.1 Screen Section

Generally the MA-03 can be operated interactively. While selecting various keys displayed on the screen, operation can be advanced.

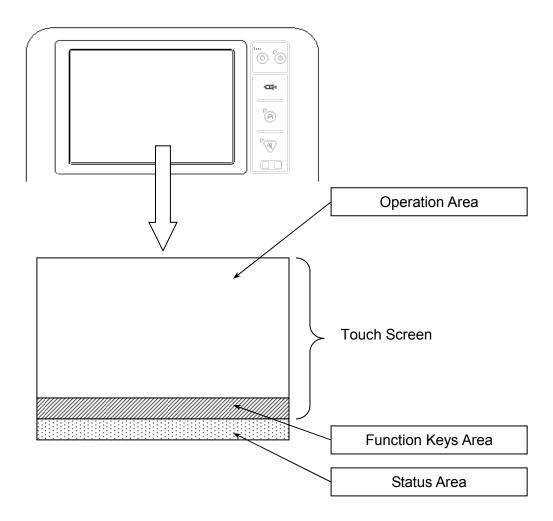


Figure 4.1 Screen Section



Do not press buttons and keys with a ballpoint pen or other sharp pointed object. This may damage the MA-03 machine.

## 4.2 Operation Area

Several keys appear in the "Operation Area", according to the mode and operating status.

#### 4.2.1 Main Keys in "Operation Area"

#### ■ Screen Operation Keys

Back displays the previous screen.

Yes displays the next screen after executing the selected mode or order.

No displays the next or previous screen after canceling the selected mode or order.

Help displays guidance related to the alarm.

#### ■ Mode Selection Keys

Install leads to the process to install the blood tubing tubing. leads to the process to rinse and priming the blood tubing. Rinsing/ Priming leads to the process to re-priming the blood tubing. Re-priming Treatment/ leads to the process to perform the treatment and to return the blood Return to the patient after treatment. Re-return leads to the process to re-return the blood to the patient. leads to the process to detach the blood tubing. Detach When the key is touched, the window to confirm the termination of tubing treatment appears.

## **WARNING**

After activating the "Detach tubing" process, the machine can no longer return to the previous process.

This key is accepted in any process from the "Procedure" screen. Do not operate this key unless the complete termination of the treatment is intended and the patient is disconnected.

#### **■** Function Instruction Keys

Cancel treatment

This key is to intentionally terminate a process of Rinsing, Priming, Treatment or Return.

When the key is touched, the window to confirm the termination of treatment appears.

## **MARNING**

Once the "Cancel Treatment" is executed, both Treatment and Return processes are disenabled to continue or execute. Do not operate this key unless a premature termination of the treatment is intended.

Continue

resumes the operation which has been suspended by the alarm.

## 4.2.2 Operational State Screen

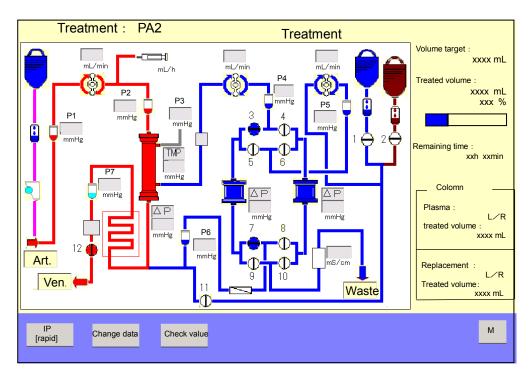


Figure 4.2: Operational State Screen

## 4.3 Function Keys Area

Function keys are displayed in the function key area, according to the operational state and mode.

The Infusion Pump works faster only when continually pressed.

Change. data

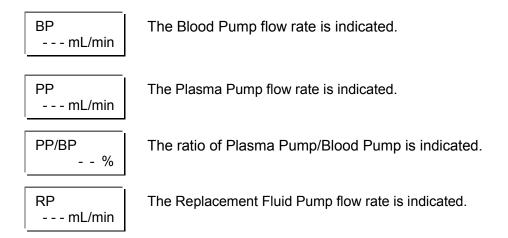
displays the screen to change setting data.

Check value

displays the screen for checking the monitoring value.

#### 4.4 Status Area

The information is indicated in the status area, according to the operational state and mode.



## 5. DATA SETTING OF THE MA-03

### **5.1 Basic Setting Procedure**

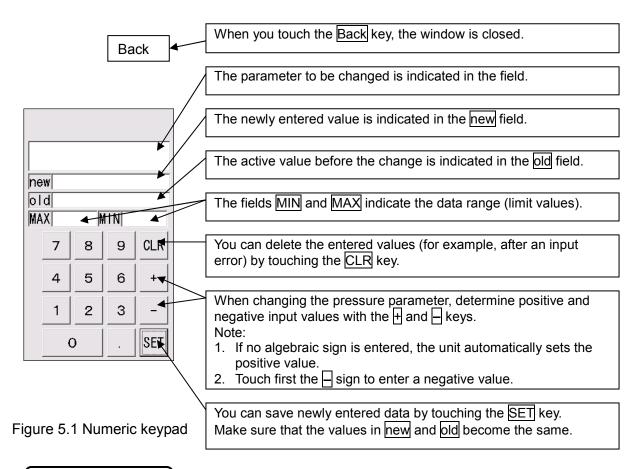
There are two ways to input or change setting values:

- 1. Input of data by using the numeric keypad
- 2. Direct change of data by turning the flow rate knob.

#### 5.1.1 Numeric keypad

When you touch the data field (parameter display) which you are to change, a new screen with a numeric keypad for data input automatically appears on the screen.

By touching the appropriate key, the following functions can be executed:



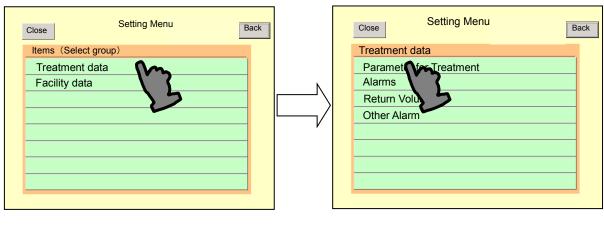


Before any treatment starts, make sure the value which is input by the numeric keypad is the same as the number in the field.

### **5.1.2 Basic Methods of Data Input**

The basic methods for data input described below is applicable to almost all data changes.

With the Data fields and keys that are specially marked by the green frame, direct change can be made.



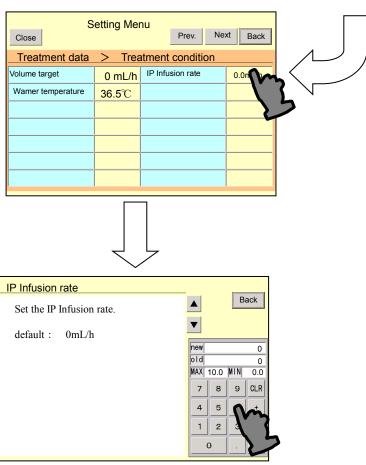


Figure 5.2 Basic Methods of Data Input

Data input/data change by example of "IP Infusion rate":

- 1. Touch the Change data key on the function key area.
- 2. Touch the Treatment data key on the "Items (Select group)" of "Setting Menu" Screen.
- 3. Touch the numeric field to the right of IP Infusion rate.
- 4. The numeric keypad will appear on the display.
- 5. Enter the required value on the numeric keypad by touching the corresponding keys. The entered value appears in the <a href="new">new</a> field.

  If the entered value is incorrect, delete the value with the <a href="CLR">CLR</a> key.
- 6. Touch the <u>SET</u> key to save the entered value. The newly stored value appears in the <u>old</u> field.



After entering a new value, make sure that the values in the new and old fields are the same.

### 5.2 Data List

## 5.2.1 Treatment data setup

An operator usually set three values of "Parameter for Treatment" before starting Treatment process.

Contents	Default value	Setting range	Unit		
Parameter for Treatment					
Volume target	0	0 ~ 20,000	mL		
IP Infusion rate	0.0	0.0 ~ 10.0	mL/h		
Blood warmer temperature	36.5	35.0 ~ 39.0	°C		
Alarms					
Arterial pressure (upper)	200	0 ~ 300	mmHg		
Arterial pressure (lower)	-170	-250 ~ 0	mmHg		
Venous pressure (upper)	170	0 ~ 300	mmHg		
Venous pressure (lower)	-50	-200 ~ 100	mmHg		
Venous pressure (Auto-upper)	60	0 ~ 100	mmHg		
Venous pressure (Auto-lower)	-40	-100 ~ 0	mmHg		
Limit value of Venous pressure alarm (Auto-lower)	10	-100 ~ 100	mmHg		
Return volume					
Blood volume in Separator	100	0 ~ 200	mL		
Plasma volume	250	0 ~ 500	mL		
Blood volume after Plasma is returned	50	0 ~ 200	mL		
Re-Return volume (Blood only)	0	0 ~ 999	mL		
Other alarm					
Separator differential pressure (upper)	100	0 ~ Limit value	mmHg		
Separator differential pressure (lower)	-50	-150 ~ 0	mmHg		
TMP (upper)	60	0 ~ Limit value	mmHg		
TMP (lower)	-50	-150 ~ 0	mmHg		
Column differential pressure (upper)	120	0 ~ Limit value	mmHg		
Column differential pressure (lower)	-60	-150 ~ 0	mmHg		



An operator must enter double-figures passwords to set the "Limit value of Venous pressure alarm (Auto-lower)", and is responsible for it.



A responsible person should set the three "Limit values" in Maintenance mode.

## 5.2.2 Facility data setup

## **A**CAUTION

An operator must enter double-figures password to set each "Facility data setup" value, and is responsible for it

Contents	Default value	Setting range	Unit		
Parameter for Facility					
Syringe calibration	20.2	14.0 ~ 24.0	mm		
Parameter for Blood flow monitor					
Insufficient Blood flow (flow rate)	20	7 ~ 40	mL/min		
Insufficient Blood flow (time)	30	0 ~ 60	sec		
BP flow limit (start/flow)	20	10 ~ 40	mL/min		
BP flow limit (start/pressure)	-70	-100 ~ -30	mmHg		
Parameter for Blood Leak Detector					
BLD alarm point	5.0	1.0 ~ 5.0	mL/L		
BLD 2nd. calibration	0 (invalid)	0 ~ 1	-		
BLD 2nd. calibration execute time	100	0 ~ 200	mL		
Sensor Valid/Invalid					
LD2 detection	0 (invalid)	0 ~ 1	-		
LD3 detection	0 (invalid)	0 ~ 1	-		
FD1 detection	1 (valid)	0 ~ 1	-		



Setting values should be within the setting range shown in the list above, and the lower limit cannot exceed the higher limit.

#### 5. DATA SETTING

## 6. TREATMENT OPERATION OF THE MA-03

This chapter provides the qualified operator with the recommended daily procedures to operate the MA-03 for regular treatment.

To operate the MA-03 for the Plasma Adsorption treatment see chapter "2. OVERVIEW".

## **6.1 Machine Preparation**

After the MA-03 is installed and preparation procedure is about to start, make sure:

- ✓ There is no deformation of the machine.
- ✓ The power cord is connected to outlet with ground terminal.
- ✓ The manual handle for the blood pump is available.

## 6.1.1 Turning on the Machine

1. Press the "POWER ON" button. (See Figure 6.1)

The green indicator lamp lights, and the "Initial" screen will appear on the LCD. (See Figure 6.2)

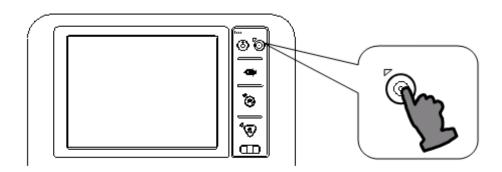


Figure 6.1 POWER ON Button on the Monitor/Operation Panel



When another treatment operation is intended, please once turn off the power and wait for more than 30 minutes, or the internal temperature may rise to generate an alarm.

### 6.1.2 Testing the Machine



Prior to the first treatment of the day, the machine performs the Start-up test to ensure its proper function.

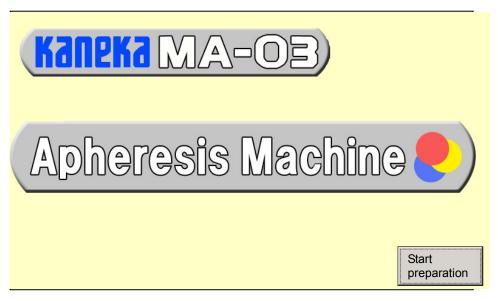


Figure 6.2 Initial Screen

1. Touch the Start preparation key on the "Initial" screen.

The "Confirmation" screen will appear on the LCD.

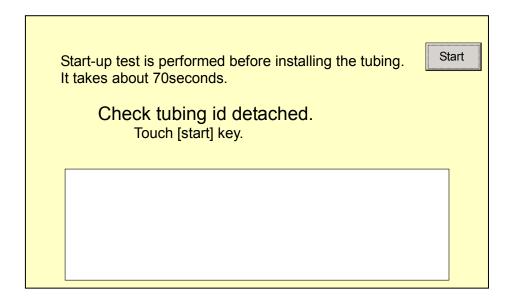


Figure 6.3 Confirmation Screen

2. Touch the Start key on the "Confirmation" screen.

The "Start-up Test" screen will appear on the LCD.

Buzzer test:

After you touch the Start key, confirm the alarm function by hearing the buzzer sound.



If the buzzer does not sound during the Start-up test, the buzzer will not sound during treatment.

In this case, do not start any treatment.

Start-up test running				
CPU test		ng time: 70 sec Buzzer sounding. Pump test Valve test	[Waiting] [Waiting]	
ROM test 3PRAM test Check data	[Waiting] [Waiting]	Transducer test US Sensor test Thermistor test	[Waiting] [Waiting] [Waiting]	
Shook data	[**************************************	Conductivity test	[Waiting]	

Figure 6.4 Start-up Test Screen

#### 6. TREATMENT OPERATION

3. The "Result of Start-up test" screen appears in the LCD when any defect or abnormality is found in the Start-up test.

Execute one of the followings by touching the Confirm key according to the guidance in the screen;

- (1) Repeat the "Start-up test",
- (2) Cancel the operation.

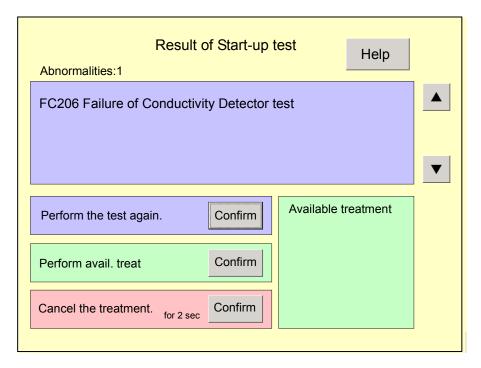


Figure 6.5 Result of Start-up Test Screen



If the machine fails the Start-up test, do not use this machine for any treatment. Contact the service person.



"Perform avail. treat" function is not available.

## **6.1.3 Selecting the Treatment Method**

After the self test completes, the "Treatment Selection 1" screen will appear on the LCD.
 Touch the key you selected.

After the key is touched, the color of the key becomes blue.

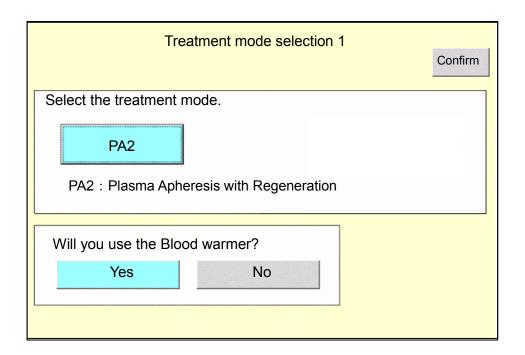


Figure 6.6 Treatment Selection 1 Screen

- Touch the key to use/not use the blood warmer on the "Treatment Selection 1" screen.
   After the key is touched, the color of the key becomes blue.
- 3. Touch the Confirm key on the "Treatment Selection 1" screen.

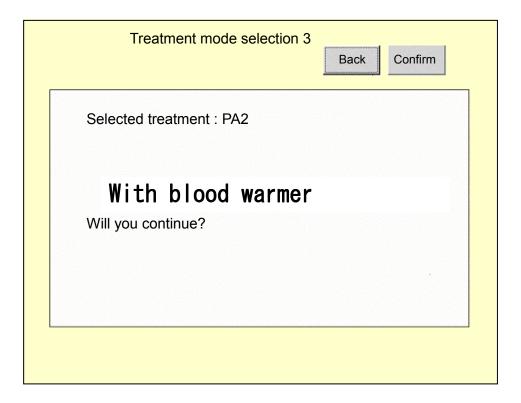


Figure 6.7 Treatment Selection3 Screen

4. Confirm the selected treatment method is displayed on the "Treatment Selection 3" screen, and touch the Confirm key.

The "Selection of Data Logging" screen appears. Close the "Selection of Data Logging" screen and the "Procedure" screen appears.



See Section 8.3.4 Data Logging for the details.

## 6.2 PA2

### 6.2.1 Install Tubing



Line map of the blood tubing for PA2 mode is directly printed on the machine surface.

1. The red lines show the blood flow.

The following shows major fluid path.

- 2. The yellow lines show the plasma flow.
- 3. The blue lines show the replacement fluid flow.
- 4. The brown lines show the regeneration fluid flow.
- 1. Touch the Install tubing key on the "Procedure" screen.

The "Install tubing" screen will appear on the LCD.

Each valve opens automatically to install the tubing.

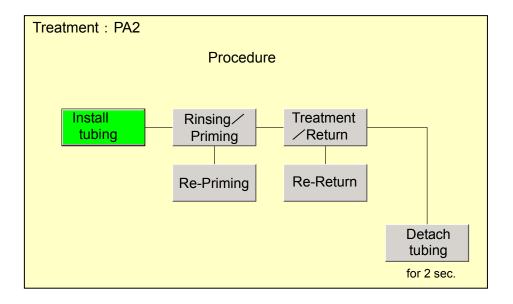


Figure 6.8 Procedure Screen

## **MARNING**

Once moved into Detach tubing process by touching the Detach tubing key, the machine can no longer return to the previous process.

This key is accepted in any process from the "Procedure" screen. Do not operate this key unless the complete termination of the treatment is intended.

#### 6. TREATMENT OPERATION

2. Install the tubing referring to the tubing diagram displayed on the "Install tubing" screen on the LCD.

To confirm the tube is properly installed, see the Figure 6.9 / 6.10 (The provided figure depends on the configuration of the MA-03.)



Confirm all connection points of blood tubing are aseptic (capped) before use.

This operation should be performed aseptically.

## **MARNING**

Do not touch the fluid in the waste container to prevent contamination.

## **A**CAUTION

While installing the tubing (Install tubing Screen is displayed), install the tubing only and make sure the Separator and Column are not attached. If the Separator or Column is attached, alarm will occur during the Rinsing/Priming process.

# **⚠** CAUTION

Do not stay on the <code>[install tubing]</code> screen for Attach <code>[tubing only]</code> for more than 30 minutes, or the internal temperature may rise to generate an alarm.

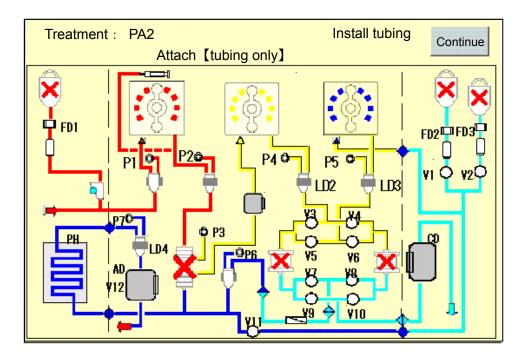


Figure 6.9 Install Tubing Screen for PA2

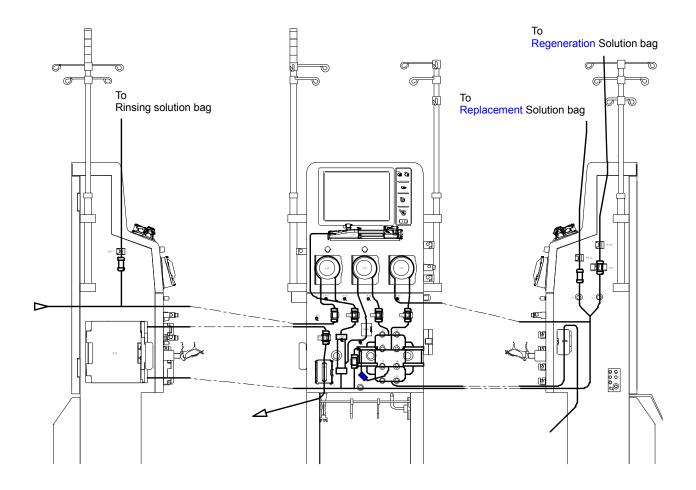


Figure 6.10 Configuration of tubing, Separator and column for PA2.

- 3. Install the pump-tube segment to each pump.
  - 1) Open the pump cover.
  - 2) Place the inlet of the pump-tube segment to the left side.
  - 3) Insert the tube between the pump rotor and stator by turning the rotor clockwise.
  - 4) Place the outlet of the pump-tube segment to the right side and close the pump cover.



Be careful not to pinch your fingers between the rotor and the stator.

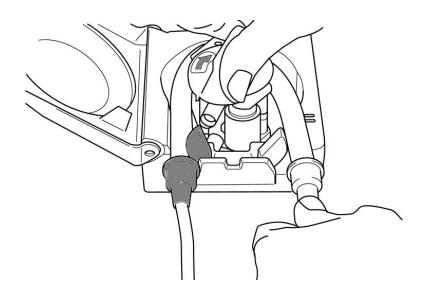


Figure 6.11 Inserting the Pump-tube Segment

# **A**CAUTION

Make sure the collar of the Pump-tube segment is positioned below the bottom of the tube clamp.

This will prevent kinking of the Pump-tube segment during the pump operation.

4. Open the Level Detector door and place each chamber into each holder and shut it with a snap.

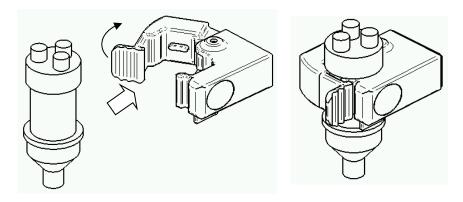


Figure 6.12 Installing the Chamber to the Level Detector

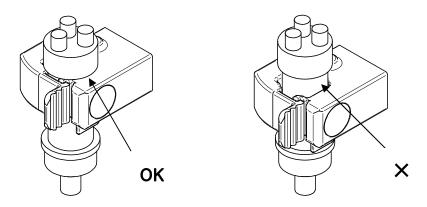


Figure 6.13 Position of the chamber

5. Open the Fluid Detector door and place each tube into each holder and shut it with a snap.

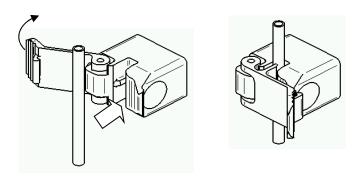


Figure 6.14 Installing the Tube to the Fluid Detector

- 6. Place the chamber into the Drip Detector.
- 7. Place each chamber into each chamber holder.
- 8. Open the Conductivity Detector door and place the detects-conductivity tube segment into the holder and shut it with a snap.

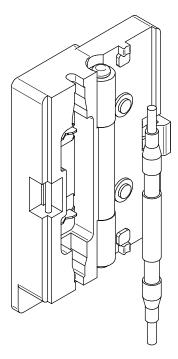


Figure 6.15 Installing the detects-conductivity tube segment into the Conductivity Detector

9. Open the Blood Leak Detector door and place the tube into the holder and shut it with a snap.

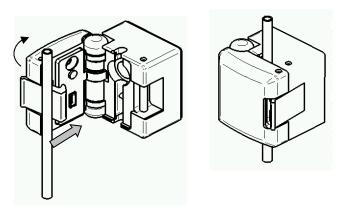


Figure 6.16 Installing the Tube to the Blood Leak Detector

10. Open the Air Detector door and place the tube into the holder and shut it with a snap.

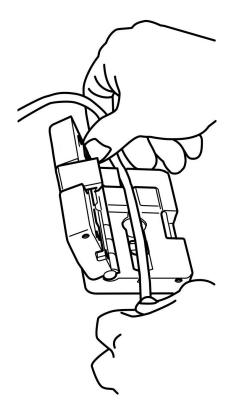


Figure 6.17 Installing the Tube to the Air Detector

- 11. Install each tube into each Valve.
  - 1) Press the holder of the Valve.
  - 2) Place the tube at the center of the Valve.
  - 3) Make sure the holder closes firmly.

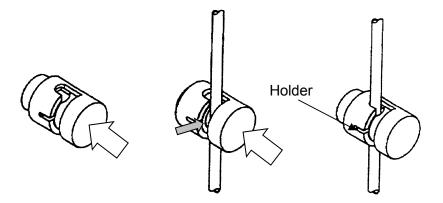


Figure 6.18 Installing the Tube to the Valve

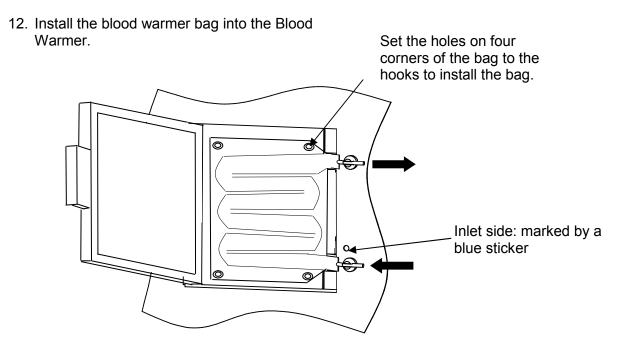


Figure 6.19 Installing the Bag to the Blood Warmer



When closing the cover of blood warmer, be careful not to pinch or bend the bag and tubes.

Place the tube in the tube holder correctly to prevent kink and blockage.

13. Connect the transducer Protective Filter to each pressure port by turning them clockwise.

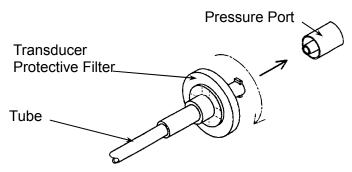


Figure 6.20 Attach the Transducer Protective Filter

# **MARNING**

If any of the external Transducer Protective Filter, internal Transducer Protective Filter or the internal transducer is bloodstained, the filter must be replaced to new one. And the transducer and the adjacent parts must be disinfected or replaced. The internal parts of machine should be exchanged or disinfected only by the person authorized by DISTRIBUTER.

#### 6. TREATMENT OPERATION

- 14. Connect the tube to the syringe, and attach the syringe to the Infusion Pump.
  - 1) Fill the syringe with heparin solution under the instructions of the physician.
  - 2) Move the slider while pressing the unlock button of the slider.
  - 3) Connect the tube of the heparin line to the syringe.
  - 4) Set the syringe into the syringe holder, by fitting the syringe collars into the channels of the holder and slider.
  - 5) Pull up the holder lever, and turn it and release it on the syringe.



Figure 6.21 Installing the Syringe to the Infusion Pump



Clamp the syringe line with a forceps in case that the tubing is not connected with a syringe before the Rinsing process is executed, or the "Leak error" alarm may occur in Rinsing process.

15. Touch the Continue key on the "Install tubing" screen.

All valves close automatically and the "Attach Disposable" screen will appear on the LCD.

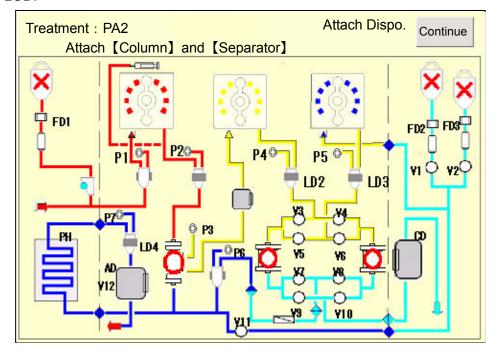


Figure 6.22 Attach Disposable Screen for PA2

- 16. Attach the separator and columns to the holders respectively.
- 17. Connect the blood tubing to the separator and columns.

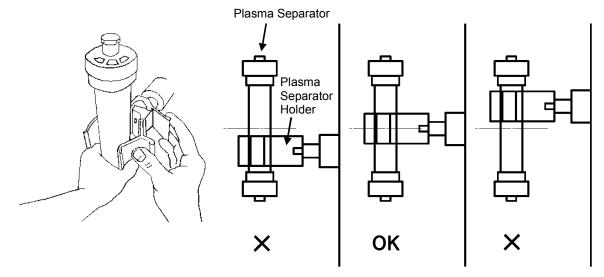


Figure 6.23 Attach the separator



While connecting tubing lines to other disposables, a careful handling is required not to spill out liquid from them.

Hold the middle or upper part of plasma separator by the holder as shown in figure 6.23. Otherwise "Span test error for P3 or P6" alarm may possibly be generated in the Rinsing process.

### 6.2.2 Rinsing and Priming

1. Touch the Continue key on the "Attach Disposable" screen.

The "Procedure" screen will appear on the LCD.

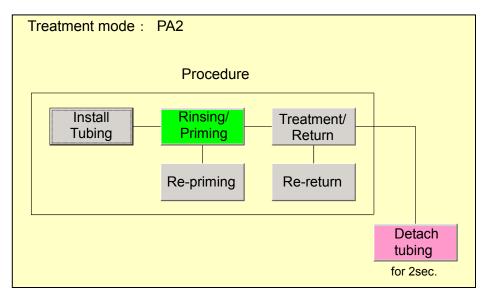


Figure 6.24 Procedure Screen



Once moved into Detach tubing process by touching the Detach tubing key, the machine can no longer return to the previous process.

This key is accepted in any process from the "Procedure" screen. Do not operate this key unless the complete termination of the treatment is intended.

## NOTICE

In case any improper installing of tubing line (e.g., a line is not installed in the valve) is found after the completion of Install Tubing process, touch the <a href="Install Tubing">Install Tubing</a> key and the "Re-install Tubing" screen appears.

On the "Install Tubing" screen, any desired valve can open with touching the corresponding valve marking on the screen, then re-install the tubing line properly.

Touch the Rinsing/Priming key on the "Procedure" screen.
 The "Preparation of Rinsing" screen will appear on the LCD.

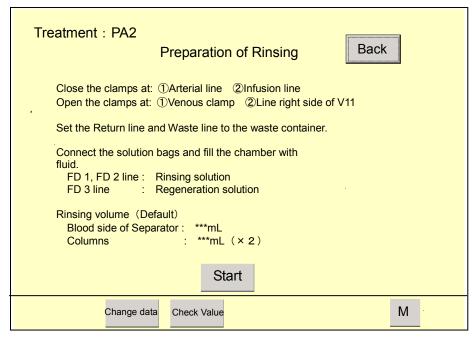


Figure 6.25 Preparation of Rinsing Screen

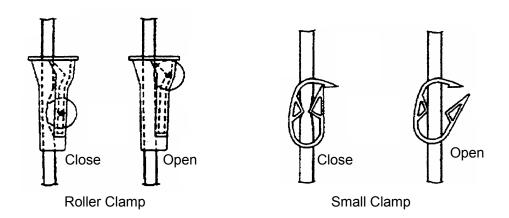


Figure 6.26 Roller Clamp and Small Clamp

- 3. Close the clamps on the arterial and infusion lines.
- 4. Open the clamps on the venous line and on the line right of V11.
- 5. Put the end of the venous and waste lines to the waste container.

# **⚠** CAUTION

Waste bags, if used, shall be hung on the hooks equipped above the Waste Fluid Container Table.

If a waste bag is placed above the valve V1, the automatic fluid level adjustment of drip chamber may not function correctly in Rinsing process.

## **A**CAUTION

In case the end of the waste line is placed closer to the floor (e.g., at closer to the bottom of the waste container), the "Column differential press.(lower)" alarm might occur.

- Hang each solution bag on each bag hanger.
- 7. Connect each tubing to each solution bag.
- 8. Fill each drip chamber on each infusion line about 1/2 by squeezing and releasing them.



To close a Roller Clamp, lower the roller to the end. If the roller stays halfway, leak may occur.

9. Touch the Start key on the "Procedure" screen.

The "Rinsing of Arterial Line" screen will appear on the LCD.

Treatment: PA2

Rinsing

Open clamps of the infusion and arterial lines.

Fill the arterial line with the saline to remove air in the line.

Close the clamp of the arterial line.

Continue

Figure 6.27 Rinsing of Arterial Line Screen.

- 10. Rinsing the arterial line manually.
  - Open the roller clamp and the small clamp on both the infusion and arterial lines, and unclamp the arterial line. Rinse the arterial line manually with rinsing solution for about 30 seconds.
  - 2) After filling the arterial line with rinsing solution, clamp the end of the arterial line with forceps.
- 11. Touch the Continue key on the "Rinsing of Arterial Line" screen.

The "Rinsing" screen will appear on the LCD.

The rinsing process starts automatically.

(Leak check starts during the rinsing process.)

Each pump starts at the fixed flow rate.

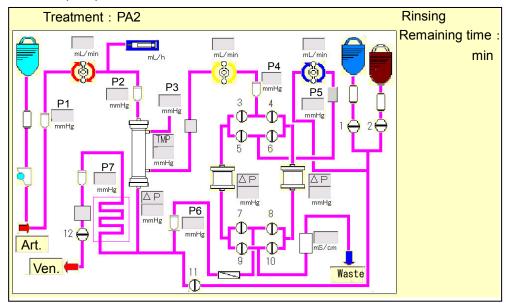


Figure 6.28 Rinsing Screen



In case any improper installing of tubing line (e.g., a tube is not properly installed in the valve) is found during Rinsing process;

- ①Press the BLOOD PUMP Button on the Operation Panel, and the machine becomes into the "Process is suspended" status. (The "Process is suspended" screen appears.)
- ②Touch the Re-install tubing key on the "Process is suspended" screen, and the "Re-install Tubing" screen appears.
- ③Touch any desired valve marking on the "Re-install Tubing" screen to open the corresponding valve opens, then, install the tubing line in the valve properly.
- (4) Confirm the tubing line is properly installed and press BLOOD PUMP Button (a) to resume Rinsing process.

During alarm generating, the install tubing key is invalid.

It becomes effective after reset alarms.

Release all alarms to reactivate the install tubing key.

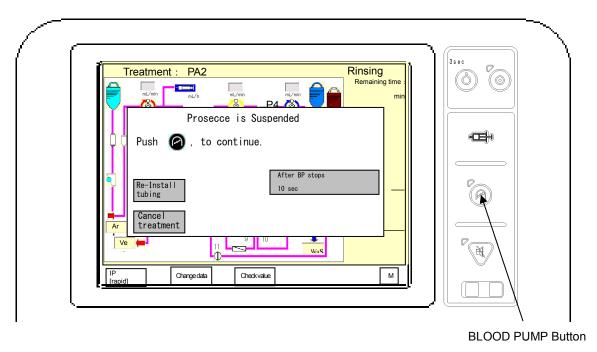


Figure 6.29 Blood PUMP BUTTON on the Operation Panel

12. When the rinsing volume reaches the preset value, each pump stops automatically.
The Preparation of "Priming" screen will appear on the LCD.

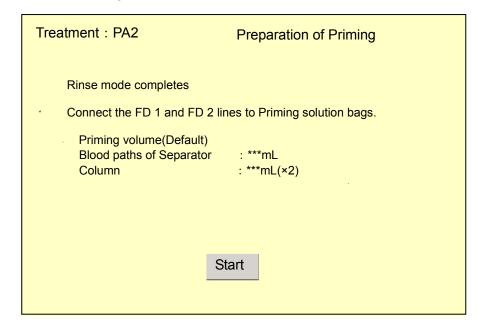


Figure 6.30 Preparation of Priming Screen

Replace rinsing solution bag to priming solution bag and touch the Start key.

The same screen as Figure 6.28 appears and Priming starts. ("Priming" screen)

13. When the priming volume reaches the preset value, each pump stops automatically.

The "Priming Completes" screen will appear on the LCD.

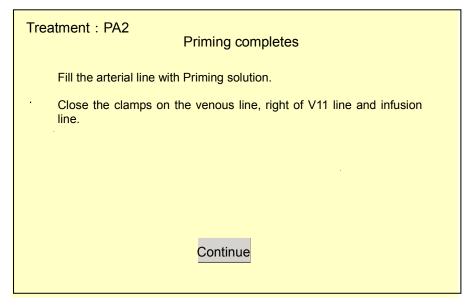


Figure 6.31 Priming completes Screen

Fill the arterial line with saline, and close the clamps on the venous and infusion line and on the line right of V11

Touch the Continue key and the "Procedure" screen appears.

The Re-Priming key appears in yellow color in the "Procedure" screen after the completion of the priming process. Touch the Re-Priming key to execute the re-priming. The device is re-primed with the same volume of priming solution as for the priming.



The MA-03 performs some of the self test during the rinsing and priming process. Depending on the result of the test, some treatment may not be started.



If the machine is turned off while any screen other than the "Procedure" screen (i.e.,

"Rinsing", "Treatment") is displayed, the machine will be in the suspended mode when turned back on, as indicated by the "Process is suspended" screen.

To resume the process, move out of the suspended status by pressing the BLOOD PUMP Button on the operation panel. (See section 6.2.3.5 for the "Process is suspended" screen)

## **MARNING**

The <u>Cancel Treatment</u> key on the "Process is suspended" screen is to intentionally terminate the process before the completion.

When this key is touched and the "Procedure" screen appears, no other key than Detach tubing key can be accepted, that is, it means the termination of whole treatment process. Never touch this key except for the case that the premature treatment-termination is intended.

#### 6.2.3 Treatment



This section shows the procedure from connection of the tubing to a patient to disconnection of the tubing after completing treatment.

Operate under the instructions of the physician.

#### 6.2.3.1 Entering the treatment data



Before starting any treatment, check the setting data for treatment on the Preparation of Treatment Screen.

## NOTICE

When the treatment completes, volume target and IP Infusion rate automatically return to the default value (0).

1. Touch the Treatment/Return key on the "Procedure" screen. The Preparation of "Treatment" screen will appear on the LCD.

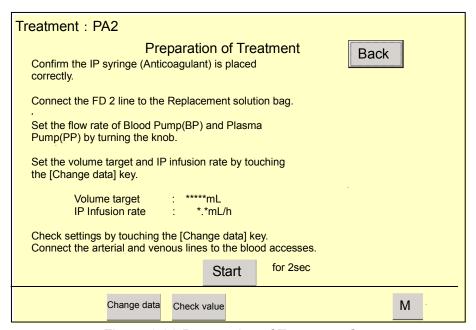


Figure 6.32 Preparation of Treatment Screen

- 2. Set the blood flow rate of the Blood Pump (BP) by turning the knob.
- 3. Set the fluid flow rate of the Plasma Pump (PP) and the Replacement Fluid Pump (RP) by turning the knob of Plasma/Replacement ratio.
  - Set the plasma flow rate as a percentage of the blood flow rate.
  - The replacement fluid rate should be the same as the plasma flow rate.
- 4. Touch the Change data key on the "Treatment" screen.
  - The "Setting Menu" screen will appear on the LCD.
  - See chapter 5 for setting the data.

### 6.2.3.2 Connection to the patient

1. After making sure the roller clamp and the small clamp on the infusion line closes, clamp the arterial and venous lines with forceps.

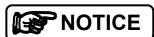
## **A**CAUTION

- 1. Confirm that the tubing and solution bags are correctly installed and connected.
- Confirm that no bubble remains in the tubing.
- 3. If any bubbles remain, tap the tube and move the bubbles to the upper part of the chamber.
- 4. Confirm that the chambers are properly filled and the transducer protective filters are not wet.
- Close the clamps on the cannula.Cannulate the patient under the instructions of the physician.
- 3. Aseptically connect one cannula to the arterial line.
- 4. Aseptically connect another cannula to the venous line.
- 5. Open the clamps on all lines except on the infusion line and on the right side of V11.
- 6. Touch the Start key on the Preparation of "Treatment" screen.

The "Treatment" screen will appear on the LCD.

### 6.2.3.3 Starting the treatment

1. The pump starts moving.



During the treatment, monitor the following:

- 1. Condition of the patient.
- 2. Operation of the machine.
- 3. No blood leak from the connected parts of the tubing, Separator and Adsorption Column(s).

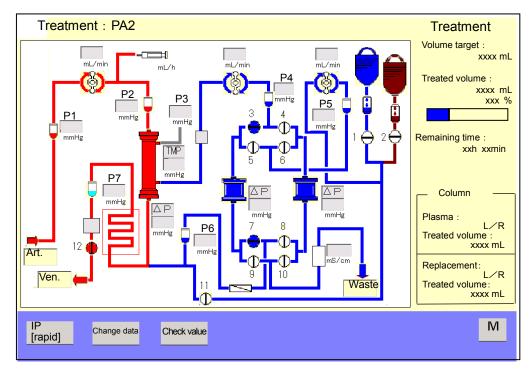


Figure 6.33 Treatment Screen

### 6.2.3.4 Monitoring the treatment

The "Check Value" screen of the MA-03 helps monitor the general status of treatment.

1. Touch the Check value key on the "Treatment" screen.

"Check" Value screen will appear on the LCD.

## 6.2.3.5 Power Failure during Treatment

In case of a power failure, all pumps stop, all valves close, and all detectors become inactive.

Alarm buzzer sounds uninterruptedly for two minutes and more, which cannot be stopped with the MUTE Button.

When main power returns, the machine becomes automatically in "Process is suspended" status (The "Process is suspended" screen appears). All pumps keep stop and all valves keep closed. To resume the treatment, push the button in the right side of the operation panel.



To stop the buzzer, keep pressing the POWER OFF Button in the right side of the operation panel for at least 3 seconds.

In this condition, even when the commercial power supply returns, the MA-03 remains power OFF.

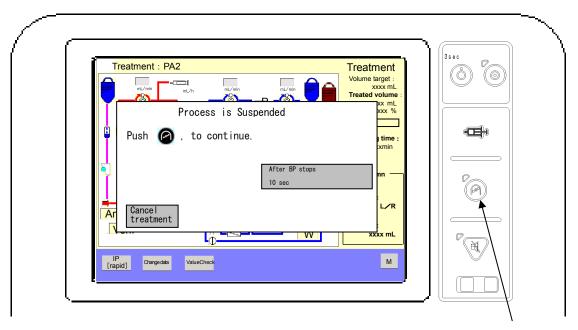


Figure 6.34 Process is Suspended Screen

**BLOOD PUMP Button** 

### 6.2.3.6 Volume target completes

When the treated plasma volume reaches the pre-set volume target, the music(by pre-set) tells the completion of the treatment and the "Volume Target Completes" screen appears on the LCD. appears.)

In case any further continuation of the treatment is desired, increase the volume target by changing data, and touch the Continue Treatment key to resume.

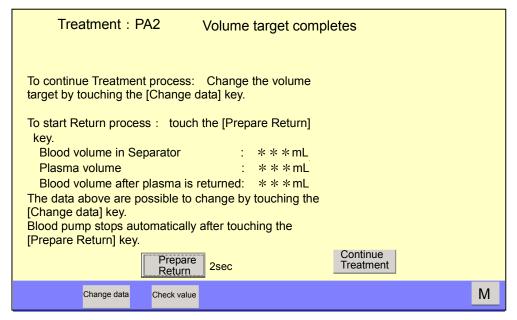


Figure 6.35 Volume Target Completes Screen

#### 6.2.4 Return

1. Touch the Prepare Return key on the "Volume target completes" screen.

The Preparation of "Return" screen will appear on the LCD.

The Blood Pump stops.

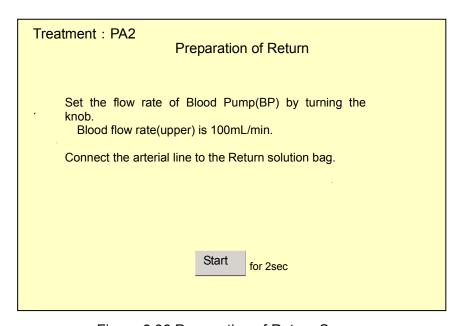


Figure 6.36 Preparation of Return Screen

- 2. Clamp the cannula and the arterial line.
- 3. Aseptically disconnect the arterial line from the cannula and connect a needle to the end of the arterial line.
- 4. Aseptically connect the arterial line to the solution bag.
- 5. Remove the infusion line from the Fluid Detector 1 (FD1) and install the arterial line instead.

6. Touch the Start key on the Preparation of "Return" screen.

The "Return" screen will appear on the LCD.

Maximum rate of Blood Pump (BP) is 100mL/min.

Return blood and plasma to the patient.

7. When the returned volume reaches the preset value, the Blood Pump stops automatically.

The "Return Completes" screen will appear on the LCD.

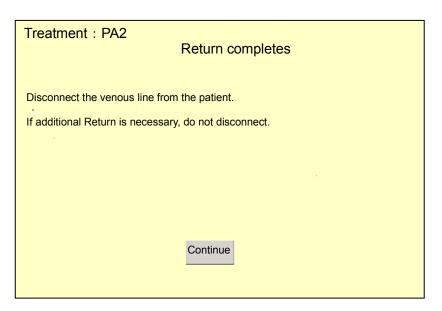


Figure 6.37 Return Completes Screen

- 8. Clamp the cannula on the venous line.
- 9. Aseptically remove the cannula from the return side of the patient.
- 10. Touch the Continue key on the "Return Completes" screen. The "Procedure" screen will appear on the LCD.

In case an additional blood return process is desired, touch the Re-Return key on the "Procedure" screen without above 8 and 9 operations.

The "Preparation of Re-Return" screen appears. Set a Re-Return volume (for "blood" side only) through the Changing data key, then touch the Start key to resume.

The Re-Return key appears in yellow color in the "Procedure" screen after the completion of Return process.



Re-Return process is applicable only to the blood side and no more plasma side is returned in Re-Return process.

### 6.2.5 Completion of the Operation

### 6.2.5.1 Disconnecting the tubing

- 1. Touch the Detach tubing key on the "Procedure" screen for 2 sec. and more, then, the confirmation window appears. Touch the YES key on the window for 2 sec. and more, then the Treatment is finished screen appears.
- 2. Disconnect the line from the solution bags.
- 3. Unclamp the roller clamp and the small clamp to open the infusion line to the atmosphere.
- 4. Put the end of the venous and waste line to the waste container.
- 5. Touch the Open valve key on "The Treatment is finished" screen.
- 6. Remove the tubing, Transducer Protective Filters, Plasma Separator, Adsorption Columns, Syringe and Solution bags.

## 6.2.6 Completion

1. Touch the Confirm key on "The Treatment is finished" screen.

The "Initial" screen will appear on the LCD.

- 2. Press the "POWER OFF" button.
- 3. Disposables (i.e., tubing, plasma separator, syringe, etc.) are to be discarded according to the local laws and regulations.
- 4. Disconnect the Mains Plug from the outlet.
- Clean or disinfect the machine according to the routine maintenance procedure described in the chapter 9.

## 7. ALARMS OF THE MA-03

#### 7.1 Alarm Status

## **⚠** WARNING

Operate the MA-03 under the instructions of the physician while carefully monitoring the patient's condition.

When the alarm related to the treatment occurs, the physician should take appropriate measures.

1. There are three kinds of alarms by type of reset.

Automatic reset: When the cause of the alarm is removed, the buzzer stops and the alarm system recovers to the normal state automatically. (The term "Auto" is mentioned on the Alarm list.)

Key reset : When the cause of the alarm is removed, touch the Continue key to

recover. (The term "Key" is mentioned on the Alarm list.)

Power on/off reset: By turning off and on the machine, the MA-03 will return to normal state. (The term "Power" is mentioned on the Alarm list.)

- 2. There are four kinds of alarms by type of operation.
  - 1) The alarm related to the blood line (The term "Blood" is mentioned on the Alarm list.)

When the alarm related to the blood line (line in which blood flows) occurs, or abnormalities of the machine are detected, this machine performs the following operation.

- a. Buzzer sounds and mute switch lamp flashes.
- b. The red indication lamp lights, and the alarm screen is displayed on the LCD.
- c. The Blood Pump (BP), Plasma Pump (PP), and Replacement Fluid Pump (RP) stop.
- d. Venous valve (V12) closes.
- 2) The alarm related to the plasma line (The term "Plasma" is mentioned on the Alarm list.)

When the alarm related to the plasma line occurs, this machine performs the following operation.

- a. Buzzer sounds and mute switch lamp flashes.
- b. The red indication lamp lights, and the alarm screen is displayed on the LCD.
- c. The Plasma Pump (PP), and Replacement Fluid Pump (RP) stop.
- 3) The alarm related to the replacement fluid line (The term "Replace" is mentioned on the Alarm list.)

When the alarm related to the replacement fluid line occurs, this machine performs the following operation.

#### 7. ALARMS

- a. Buzzer sounds and mute switch lamp flashes.
- b. The red indication lamp lights, and the alarm screen is displayed on the LCD.
- c. The Replacement Fluid Pump (RP) stops.

## 7.2 Alarm display

#### 1. Buzzer sound

When alarm occurs, buzzer sounds to attract attention. The buzzer can be temporarily turned off, when the mute switch is pressed.



Press the MUTE button, to turn off the buzzer. (The preset time for the buzzer to stop is two minutes.)

The volume of the buzzer can be changed.

#### 2. Lighting of indication lamp

External lamp shows four alarm states.

#### [States of external lamp]

States of indication lamp		n lamp	States of alarm
Abnormal (Red)	Complete (Yellow)	Normal (Green)	
Lighting			The computer etc. is not operating normally.
Flashing			The alarm which should be handled immideately occurs.
	Flashing		It shows the operation has completed.
		Flashing	It shows the suspension of the process or restriction of the pump.

#### 3. Display on the LCD

If an alarm occurs, the alarm screen will appear on the LCD.

The following classification number is allocated to the head of alarm messages.

- Treatment- related alarms (TRxxx ------)
- Function check alarms (FCxxx ------)

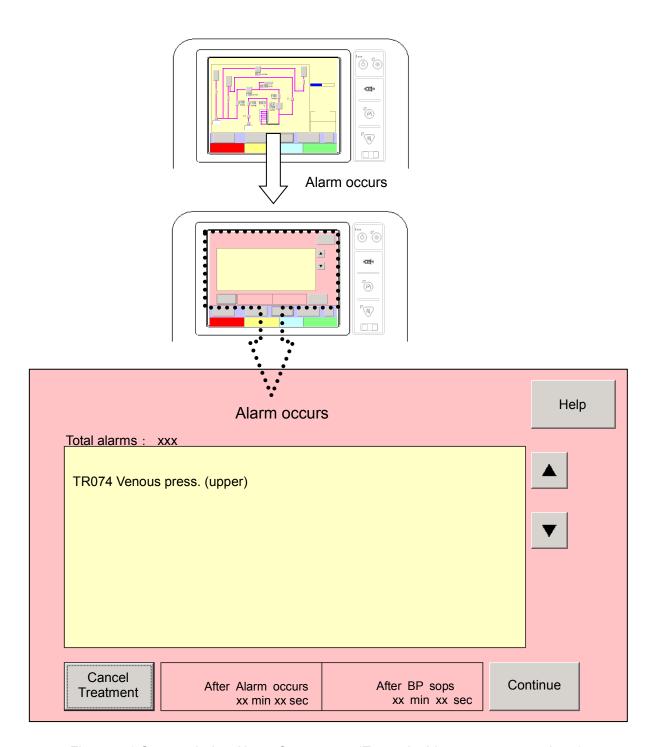


Figure 7.1 Screen during Alarm Occurrence (Example: Venous pressure alarm)



Once the "Cancel Treatment" is executed, both Treatment and Return processes are unable to continue or execute. Do not operate this key unless a premature termination of the treatment is intended.

## 7.3 Alarm point about pressure

- 1. There are three kinds of upper / lower limits of the alarm points about the pressure.
  - Automatically set alarm (only for venous pressure)
     The upper and lower points of automatically preset alarms width start monitoring the pressure after a lapse of preset time.
     Automatically preset alarm width cannot be set lower than its lower limit .
  - 2) Fixed alarm
    The presettable upper and lower points of fixed alarms work until the automatically preset alarm width is settled (automatically).
  - Critical alarm
     The upper and lower points of the critical alarms which cannot be changed .

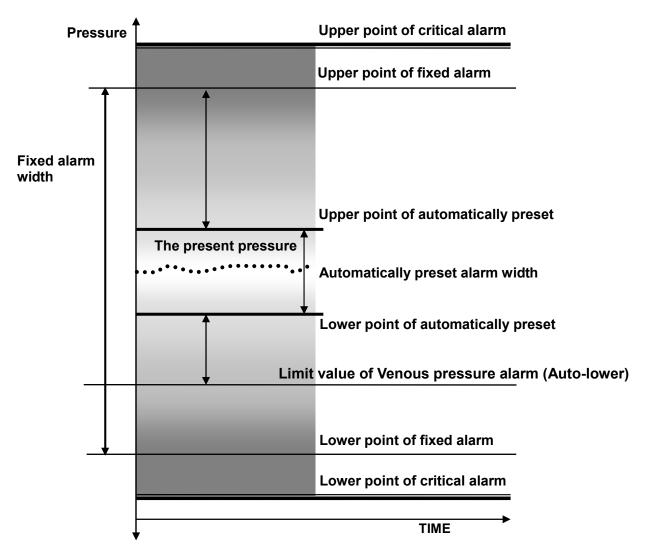


Figure 7.2 Pressure related Alarm points

## 7.4 Troubleshooting

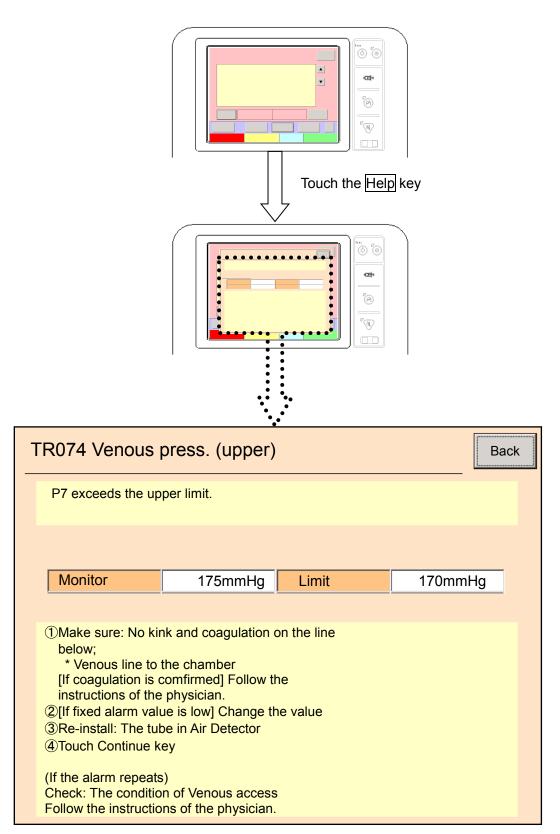


Figure 7.3 Guidance Screen (Example: Venous pressure alarm)

# **⚠** WARNING

Treatment should not be resumed until the cause of the alarm is cleared and the message disappears.

The screen is displayed by touching the Help key.

The screen consists of four frames.

- Message
- Message Description
- Display of monitored value
- Check and Measure

#### Message

The message frame shows the message on the alarm screen.

#### ■ Message Description

The message overview is the brief explanation of the message.

#### ■ Display of monitored value

The monitored contents are displayed.

#### Check and Measure

The recommended measures are displayed. Some patient-oriented treatment that is not mentioned here may be required.



If the alarm cannot be reset after recommended procedure is taken, follow the instructions of the physician and contact the service person.

## 7.5 The recovery procedure to an alarm

#### 7.5.1 Alarm related to Treatment

#### Air detector

[TR001 Bubble]

[TR002 Micro Bubble]

#### Check and Measure

- 1) Clamp the tube at outlet of the detector with clamp.
- 2) Open the door of the detector and make air bubbles in the tube flow up to Venous chamber(LD4) and close the door.
- 3) Detach the clamp from the tube.



Opening the door of the air detector is necessary to cancel alarm condition and restart treatment.

### Arterial pressure

[TR003 Arterial press.(critical lower)]

[TR004 Arterial press.(critical upper)]

[TR005 Arterial press.(lower)]

【TR006 Arterial press.(upper)】

#### **Check and Measure**

- 1) Make sure: No kink of the line below; Withdrawal line to the chamber
- 2) The roller clamp on the FD1 line is open. (for Rinsing)
- 3) Open: Pressure port P1

[If P1 gets around 0mmHg] Touch Continue key.

#### Blood/Saline Detector

[TR009 Detection of blood]

Check and Measure

[If blood is not running]

1) Clean: The tube and sensor

#### Blood flow rate

[TR010 Low flow rate(BP)]

#### **Check and Measure**

- 1) [If the upper limit of Venous pressure alarm is low] Raise: the set value
- 2) Make sure: No kink of the tube of the line below; Arterial / Venous line
- 3) Make sure: No coagulation in the line below; Arterial access to Arterial chamber
- 4) [If BP flow rate is too low] Raise: the rate by turning the knob.

#### **Blood Inlet Pressure**

[TR011 Blood inlet press.(critical lower)]
[TR012 Blood inlet press.(critical upper)]

#### Check and Measure

- 1) Make sure: No kink of the tube below; Chamber to Venous chamber(P7)
- 2) Make sure: No kink and pinch of the tube below; Inlet/outlet of Blood Warmer
- 3) Open: Pressure port P2 [If P2 gets around 0mmHg] Touch Continue key.

#### **Blood Leak Detector**

[TR017 Blood leak]

**Check and Measure** 

1) Make sure: There is no leak or hemolysis on the tube below; [If not confirmed] Clean the sensor and the tube.



If confirmed the blood leak, follow the instructions of the physician.

# **A**CAUTION

Avoid direct sunlight for the placement of the machine because exposure to the front panel of the machine by direct sunlight may cause an alarm of Blood Leak Detector.

## Pump Cover

[TR018 BP cover open]

[TR059 PP cover open]

[TR068 RP cover open]

**Check and Measure** 

1) Close: The cover

2) Make sure: No pinch below; Inlet / outlet of BP, Around the rotor

## Column Differential pressure

[TR020 Column(L) differential press.(upper)]

【TR021 Column(L) differential press.(lower)】

【TR022 Column(R) differential press.(upper)】

【TR023 Column(R) differential press.(lower)】

#### Check and Measure

- 1) Make sure: No kink and coagulation of tube
- 2) Make sure: No wet and leak of filter

[If confirmed] Attach a new filter adjust fluid, Level in the chamber.

3) Check: Connection of tube



If coagulation is confirmed, follow the instructions of the physician.

#### Fluid detector

【TR026 Fluid empty(FD1)】

【TR027 Fluid empty (FD2)】

【TR028 Fluid empty (FD3)】

#### Check and Measure

- 1) [If the solution bag is empty] Attach a new bag.
- 2) [If the solution bag is not empty]

Remove air: Air in the tube to the solution bag

Re-install: The tube Touch Continue key.

#### **Blood Warmer**

[TR029 Warmer bag uninstalled]

#### Check and Measure

1) Attach: Warmer bag to Blood Warmer

#### **Level Detector**

【TR030 Low level(LD1)】

[TR031 Low level(LD2)]

[TR032 Low level(LD3)]

[TR033 Low level(LD4)]

#### Check and Measure

1) [If the fluid level in the chamber is low]

Raise: Fluid level, Make sure: There is no kink or leak on the tube

2) [If the level is adequate]

Remove air: Move air to the upper part of the chamber.

Reattach: The chamber to the detector



If the Low level (LD3) alarm occur during rinsing, V1 can open by V1 key that is displayed on the alarm guidance screen.

### Conductivity Detector

#### [TR034 Conductivity error 1(Regeneration solution)]

#### Check and Measure

1) Check: Status of attachment below

Kink of the tube from Regeneration solution bag to Conductivity Detector

The tube on V1 and 2

[When Re-install the tube to the valve] Touch Re-Install tubing key

2) Check: Status of the connection and clamp below;

FD3 line to Regeneration solution bag

The clamp on the right of the V11 line is open.

3) Re-install: Conductivity sensor

[If the sensor is empty] Fill the line from the filter for Columns to the sensor with saline.

#### [TR035 Conductivity error 2(Rinsing solution)]

#### **Check and Measure**

1) Check: Connection below;

FD2 line to Rinsing solution bag

#### 【TR036 Priming solution error】

#### Check and Measure

1) Check: Connection below;

FD2 line to Priming solution bag

#### [TR037 Regeneration solution error]

#### Check and Measure

1) Check: Connection below;

FD3 line to Regeneration solution bag

2) Check: Install of the tubing below;

V1 to V10 respectively

3) Re-install: Conductivity Detector(CD)

[TR038 Abnormal conductivity]

[TR039 Serious abnormality of conductivity]

**Check and Measure** 

1) Check: Connection below; Replacement solution bag to the FD2 line

- 2) Make sure: No coagulation in Waste line and the conductivity sensor in the detector [If confirmed] Rinse it out of the waste line
- 3) Check: Installing of the tubing below V1 to V10 respectively

#### Plasma Inlet Pressure

【TR040 Plasma inlet press.(critical lower)】

[TR041 Plasma inlet press.(critical upper)]

Check and Measure

1) Open: Pressure port P4 [If P4 gets around 0mmHg] Touch Continue key

#### Plasma Outlet Pressure

【TR046 Plasma outlet press.(critical lower)】

[TR047 Plasma outlet press.(critical upper)]

Check and Measure

1) Open: Pressure port P6

[If P6 gets around 0mmHg] Touch Continue key.

#### Plasma Pressure

【TR052 Plasma press.(critical lower)】

[TR053 Plasma press.(critical upper)]

Check and Measure

- 1) Make sure: No clogging and coagulation in Separator
- 2) Open: Pressure port P3

[If P3 gets around 0mmHg] Touch Continue



If coagulation is confirmed, follow the instructions of the physician.

#### **Blood Warmer Cover**

[TR058 Blood Warmer cover open]

#### Check and Measure

1) Check: The cover is ajar.
[If confirmed] Close the cover firmly

2) [If the pressure in the bag is high]

Open Air Detector to release the pressure.

3) Make sure: No pinch below; Inlet/outlet of Blood Warmer

## Separator Differential Pressure

[TR060 Separator differential press.(upper)]

[TR061 Separator differential press.(lower)]

#### Check and Measure

- 1) Make sure: No kink and coagulation of the line below; Chamber to Venous chamber(P7)
- 2) Make sure: No wet and leak below; Air filter of P6(Plasma outlet pressure port) [If confirmed] Attach a new filter and adjust fluid level in the chamber(P6).
- 3) Make sure: No kink and pinch below; Inlet/outlet of Blood Warmer



If coagulation is confirmed, as clogging may occur, follow the instructions of the physician.

## Replacement Fluid Pressure

[TR062 Replacement fluid press.(critical lower)]

[TR063 Replacement fluid press.(critical upper)]

#### Check and Measure

- 1) Make sure: No kink of the line
- 2) Open: Pressure port P5

[If P5 gets around 0mmHg] Touch Continue

#### **TMP**

[TR069 TMP(upper)]
[TR070 TMP(lower)]

#### Check and Measure

- 1) Make sure: No clogging below; Separator
- 2) Make sure: No coagulation in the tube below;

Chamber to Venous chamber(P7)

- 3) Make sure: No wet and leak below; Air filter of P3(Plasma pressure port) [If confirmed] Attach a new filter and adjust fluid level in the chamber.
- 4) Make sure: No kink of the line below; Chamber to Venous chamber(P7)
- 5) Make sure: No kink and pinch below; Inlet/outlet of Blood Warmer



If coagulation or possibility of clogging is confirmed, follow the instructions of the physician.

#### Venous Pressure

【TR071 Venous press.(critical lower)】

[TR072 Venous press.(critical upper)]

#### Check and Measure

- 1) Make sure: No kink on the line below; Venous line to Chamber
- 2) Re-install: The tube in Air Detector
- 3) Open: Pressure port P7

[If P7 gets around 0mmHg] Touch Continue key.

【TR073 Venous press.(lower)】

【TR075 Venous press.(Auto-lower)】 Check and Measure

- 1) Check: Venous access
- 2) Check: Connections below; Column outlet, Separator outlet, Blood Warmer outlet/inlet, Outlet/inlet of the filter for
- 3) Make sure: No leak in the line below; V9.10 to V12, Air Detector to Venous line



If the condition is not proper, follow the instructions of the physician.

[TR074 Venous press.(upper)]

【TR076 Venous press.(Auto-upper)】

Check and Measure

- 1) Make sure: No kink and coagulation on the tube below; Venous line to Chamber
- 2) [If fixed alarm value is low] Change the value
- 3) Re-install: The tube in the Air Detector



If coagulation or possibility of clogging is confirmed, follow the instructions of the physician.

#### **Tube detector**

【TR078 No tube in the BLD】 【TR079 No tube in the AD】

**Check and Measure** 

1) Re-install: The tube in Air Detector or BLD

### Warmer bag leak detector

[TR080 Warmer bag leak]

Check and Measure

1) Check: Fluid leak from warmer bag.

[If not confirmed] Clean the sensor equipped to the bottom of Blood Warmer.



If confirmed the leakage, follow the instructions of the physician.

#### 7.6 Manual Blood Return

If the MA-03 cannot be operated normally during the treatment because of power failure, machine failure, or other causes, the RETURN process can be accomplished manually by using the manual pump handle.

# **MARNING**

This measure should be performed under the instructions of the physician while carefully monitoring the patient's condition.

All alarms are inoperable, including the air detector.

Visually inspect the venous line, and make sure bubbles are not infused into the patient.

The venous valve (V12) is equipped in the air detector (AD). Please open the door of the air detector and be sure to remove the tube from the air detector.

# **⚠** CAUTION

In order to return the blood manually, the treatment must be canceled.

Only blood in the arterial and venous lines is returned manually.

The manual blood return procedure is shown below:

- 1. Press the "POWER OFF" button. (The power failure buzzer stops.)
- 2. Clamp the cannula tube and remove the cannula from the withdrawal side of the patient .
  - Connect the arterial line to the return solution bag.
- 3. Remove the tube from the Air detector (AD).
- 4. Open the Blood Pump cover.
- 5. Attach the manual pump handle.
- 6. Slowly turn the Blood Pump handle clockwise.
- 7. When the blood return is completed, clamp the cannula tube and remove the cannula from the return side of the patient.

## 7.7 Alarm list

## 7.7.1 Alarm related to Treatment (TRxxx)

TR No.	Alarm name	Re-start method	Alarm group	Note
TR001	Bubble	Key	Blood	Bubble was detected by Air Detector.
TR002	Micro bubble	Key	Blood	Micro bubble was detected by Air Detector.
TR003	Arterial press. (critical lower)	Key	Blood	P1 exceeds the critical lower limit.
TR004	Arterial press.(critical upper)	Key	Blood	P1 exceeds the critical upper limit.
TR005	Arterial press. (lower)	Key	Blood	P1 exceeds the lower limit.
TR006	Arterial press. (upper)	Key	Blood	P1 exceeds the upper limit.
TR009	Detection of blood	Key	Blood	Blood was detected by the Blood detector.
TR010	Low flow rate (BP)	Key	Blood	Flow rate increases too slowly.
TR011	Blood inlet press. (critical lower)	Key	Blood	P2 exceeds the critical lower limit.
TR012	Blood inlet press. (critical upper)	Key	Blood	P2 exceeds the critical upper limit.
TR017	Blood leak	Key	Blood	Blood leak is detected.
TR018	BP cover open	Auto	Blood	The BP cover is open.
TR020	Column(L) differential press.(upper)	Key	Plasma	Column(L) differential pressure exceeds the upper limit.
TR021	Column(L) differential press.(lower)	Key	Plasma	Column(L) differential pressure exceeds the lower limit.
TR022	Column(R) differential press.(upper)	Key	Plasma	Column(R) differential pressure exceeds the upper limit.
TR023	Column(R) differential press. (lower)	Key	Plasma	Column(R) differential pressure exceeds the lower limit.
TR026	Fluid empty(FD 1)	Key	Blood	Bag is empty.
TR027	Fluid empty(FD 2)	Key	Replace.	Bag is empty.
TR028	Fluid empty(FD 3)	Key	Replace.	Bag is empty.
TR029	Warmer bag uninstalled	Key	Blood	Blood warm bag is not installed.
TR030	Low Level(LD 1)	Key	Blood	Fluid level of blood inlet chamber is low.
TR031	Low level (LD 2)	Key	Plasma	Fluid level of plasma inlet chamber is low.

TR No.	Alarm name	Re-start method	Alarm group	Note
TR033	Low level(LD 4)	Key	Blood	Fluid level of venous chamber is low.
TR034	Conductivity error 1 (Regeneration solution)	Key	Blood	The conductivity is low.
TR035	Conductivity error 2(Rinsing solution)	Key	Blood	Conductivity is high.
TR036	Priming solution error	Key	Blood	Conductivity is high.
TR037	Regeneration solution error	Key	Blood	Abnormal conductivity of Regene. solution (during Regene. step).
TR038	Abnormal conductivity	Key	Blood	Abnormal conductivity of Replacement solution (after Replacement step).
TR039	Serious abnormality of conductivity	Key	Blood	The abnormalities may remain unsolved.
TR040	Plasma inlet press. (critical lower)	Key	Plasma	P4 exceeds the critical lower limit.
TR041	Plasma inlet press. (Critical upper)	Key	Plasma	P4 exceeds the critical upper limit.
TR046	Plasma outlet press. (critical lower)	Key	Plasma	P6 exceeds the critical lower limit.
TR047	Plasma outlet press. (critical upper)	Key	Plasma	P6 exceeds the critical upper limit.
TR052	Plasma press. (critical lower)	Key	Plasma	P3 exceeds the critical lower limit.
TR053	Plasma press. (critical upper)	Key	Plasma	P3 exceeds the critical upper limit.
		1.7		
TR058	Blood warmer cover open	Key	Blood	The cover is ajar.
TR059	PP cover open	Auto	Plasma	The PP cover is open.
TR060	Separator differential press. (upper)	Key	Blood	Separator differential press. exceeds the upper limit.
TR061	Separator differential press. (lower)	Key	Blood	Separator differential press. exceeds the lower limit.
TR062	Replace. fluid press. (critical lower)	Key	Replace.	P5 exceeds the critical lower limit.
TR063	Replace. fluid press. (critical upper)	Key	Replace.	P5 exceeds the critical upper limit.
TR068	RP cover open	Auto	Replace.	The RP cover is open.
TR069	TMP (upper)	Key	Plasma	TMP exceeds the upper limit.
TR070	TMP (lower)	Key	Plasma	TMP exceeds the lower limit.

TR No.	Alarm name	Re-start method	Alarm group	Note
TR071	Venous press.(critical lower)	Key	Blood	P7 exceeds the critical lower limit.
TR072	Venous press.(critical upper)	Key	Blood	P7 exceeds the critical upper limit.
TR073	Venous press. (lower)	Key	Blood	P7 exceeds the lower limit.
TR074	Venous press.(upper)	Key	Blood	P7 exceeds the upper limit.
TR075	Venous press. (Auto-lower)	Key	Blood	P7 exceeds the lower limit.
TR076	Venous press. (Auto-upper)	Key	Blood	P7 exceeds the upper limit.
TR078	No tube in BLD	Auto	Blood	The tube is not detected.
TR079	No tube in AD	Auto	Blood	The tube is not detected.
TR080	Warmer bag leak	Key	Blood	The blood warmer leaks.

## 7.7.2 Function check alarm (FCxxx)

FC	Alarm name	Re-start	Alarm	Note
No.		method	group	
FC001	Add. error exception, load (CTR)	Power	Blood	CPU failure (Control)
FC002	Add. error exception, store(CTR)	Power	Blood	CPU failure (Control)
FC003	Bus error exception, instruction (CTR)	Power	Blood	CPU failure (Control)
FC004	Bus error exception, data (CTR)	Power	Blood	CPU failure (Control)
FC005	System call exception(CTR)	Power	Blood	CPU failure (Control)
FC006	Break point exception (zero division) (CTR)	Power	Blood	CPU failure (Control)
FC007	Reserve instruction exception (CTR)	Power	Blood	CPU failure (Control)
FC008	Coprocessor unusable exception (CTR)	Power	Blood	CPU failure (Control)
FC009	Over flow exception (CTR)	Power	Blood	CPU failure (Control)
FC010	3PRAM command failure(CTR)	Power	Blood	CPU failure (Control)
FC011	3PRAM sum failure(CTR)	Power	Blood	CPU failure (Control)
FC012	3PRAM timeout failure(CTR)	Power	Blood	CPU failure (Control)
FC013	3PRAM ack failure(CTR)	Power	Blood	CPU failure (Control)
FC014	3PRAM key failure(CTR)	Power	Blood	CPU failure (Control)
FC015	3PRAM read failure(CTR)	Power	Blood	CPU failure (Control)
FC016	3PRAM address failure(CTR)	Power	Blood	CPU failure (Control)
FC017	TASK2 Error(CTR)	Power	Blood	CPU failure (Control)
FC018	TASK3 Error(CTR)	Power	Blood	CPU failure (Control)
FC019	TASK4 Error(CTR)	Power	Blood	CPU failure (Control)
FC020	TASK5 Error(CTR)	Power	Blood	CPU failure (Control)
FC021	TASK6 Error(CTR)	Power	Blood	CPU failure (Control)

FC No.	Alarm name	Re-start method	Alarm group	Note
FC022	TASK7 Error(CTR)	Power	Blood	CPU failure (Control)
FC023	TASK8 Error(CTR)	Power	Blood	CPU failure (Control)
FC024	TASK9 Error(CTR)	Power	Blood	CPU failure (Control)
FC025	TASK10 Error(CTR)	Power	Blood	CPU failure (Control)
FC026	Time Base Error(CTR)	Power	Blood	CPU failure (Control)
FC027	Process select failure (CTR)	Power	Blood	CPU failure (Control)
FC028	Treatment mode failure(CTR)	Power	Blood	CPU failure (Control)
FC029	Discrepancy of page (CTR)	Power	Blood	CPU failure (Control)
FC030	No response of step transit (PRT)	Power	Blood	CPU failure (Protective)
FC031	Discrepancy of step transit (CTR)	Power	Blood	CPU failure (Control)
FC032	Alarm status failure (CTR)	Power	Blood	CPU failure (Control)
FC033	Discrepancy of treated volume(CTR)	Power	Blood	Control CPU detect the differential treated volume just a transit process.
FC034	Select key failure (CTR)	Power	Blood	CPU failure (Control)
F0026	Failure of the CDU toot (CTD)	Damer	Disad	CDU failure (Control)
FC036	Failure of the CPU test (CTR)	Power	Blood	CPU failure (Control) [FRAM abnormal]
FC037	FRAM write error(CTR)	Power	Blood	abnormal writing.
FC038	Failure of the RAM test (CTR)	Power	Blood	[FRAM abnormal] Test failure.
FC039	Failure of ROM test (CTR)	Power	Blood	[ROM abnormal] Test failure.
FC040	Abnormal 5V (CTR)	Power	Blood	[Machine failure] Incorrect voltage
FC041	Abnormal 12V (CTR)	Power	Blood	[Machine failure] Incorrect voltage
FC042	BP volume discrepancy(CTR)	Power	Blood	Control CPU detects discrepancy in BP treated volume.
FC043	PP volume discrepancy(CTR)	Power	Blood	Control CPU detects discrepancy in PP treated volume.
FC044	RP volume discrepancy(CTR)	Power	Blood	Control CPU detects discrepancy in RP treated volume.
FC045	BP volume discrepancy (PRT)	Power	Blood	Protective CPU detects discrepancy in BP treated volume.
FC046	PP volume discrepancy (PRT)	Power	Blood	Protective CPU detects discrepancy in PP treated volume.
FC047	RP volume discrepancy (PRT)	Power	Blood	Protective CPU detects discrepancy in RP treated volume.

FC No.	Alarm name	Re-start method	Alarm group	Note
FC048	Step transit failure(CTR)	Power	Blood	CPU failure (Control)
FC049	Step transit failure(PRT)	Power	Blood	CPU failure (Protective)
FC051	Add. error exception, load(PRT)	Power	Blood	CPU failure (Protective)
FC052	Add. error exception, store(PRT)	Power	Blood	CPU failure (Protective)
FC053	Bus error exception, instruction(PRT)	Power	Blood	CPU failure (Protective)
FC054	Bus error exception, data(PRT)	Power	Blood	CPU failure (Protective)
FC055	System call exception(PRT)	Power	Blood	CPU failure (Protective)
FC056	Break point exception (zero division) (PRT)	Power	Blood	CPU failure (Protective)
FC057	Reserve instruction exception (PRT)	Power	Blood	CPU failure (Protective)
FC058	Coprocessor unusable exception (PRT)	Power	Blood	CPU failure (Protective)
FC059	Over flow exception (PRT)	Power	Blood	CPU failure (Protective)
FC060	3PRAM command failure(PRT)	Power	Blood	CPU failure (Protective)
FC061	3PRAM sum failure(PRT)	Power	Blood	CPU failure (Protective)
FC062	PRAM timeout failure(PRT)	Power	Blood	CPU failure (Protective)
FC063	3PRAM ack failure(PRT)	Power	Blood	CPU failure (Protective)
FC064	3PRAM key failure(PRT)	Power	Blood	CPU failure (Protective)
FC065	3PRAM read failure(PRT)	Power	Blood	CPU failure (Protective)
FC066	3PRAM address failure(PRT)	Power	Blood	CPU failure (Protective)
FC067	TASK2 Error(PRT)	Power	Blood	CPU failure (Protective)
FC068	TASK3 Error(PRT)	Power	Blood	CPU failure (Protective)
FC069	TASK4 Error(PRT)	Power	Blood	CPU failure (Protective)
FC070	TASK5 Error(PRT)	Power	Blood	CPU failure (Protective)
FC071	TASK6 Error(PRT)	Power	Blood	CPU failure (Protective)
FC072	TASK7 Error(PRT)	Power	Blood	CPU failure (Protective)
FC073	TASK8 Error(PRT)	Power	Blood	CPU failure (Protective)
FC074	TASK9 Error(PRT)	Power	Blood	CPU failure (Protective)
FC075	TASK10 Error(PRT)	Power	Blood	CPU failure (Protective)
FC076	Time Base Error(PRT)	Power	Blood	CPU failure (Protective)
FC077	Process select failure (PRT)	Power	Blood	CPU failure (Protective)
FC078	Treatment mode failure (PRT)	Power	Blood	CPU failure (Protective)
FC079	Discrepancy of page (PRT)	Power	Blood	CPU failure (Protective)
FC080	No response of step transit (CTR)	Power	Blood	CPU failure (Control)
FC081	Discrepancy of step transit (PRT)	Power	Blood	CPU failure (Protective)
FC082	Alarm status failure (PRT)	Power	Blood	CPU failure (Protective)
FC083	Discrepancy of treated volume(PRT)	Power	Blood	CPU failure (Protective)

FC No.	Alarm name	Re-start method	Alarm group	Note
FC084	Select key failure (PRT)	Power	Blood	CPU failure (Protective)
FC086	Failure of CPU test (PRT)	Power	Blood	CPU failure (Protective)
FC087	FRAM write error (PRT)	Power	Blood	Abnormal write to the data memory (Protective)
FC088	Failure of RAM test (PRT)	Power	Blood	Failure of the data memory (Protective)
FC089	Failure of ROM test (PRT)	Power	Blood	Failure of the ROM (Protective)
FC090	Abnormal 5V (PRT)	Power	Blood	[Machine failure] Incorrect voltage (Protective)
FC091	Abnormal 12V (PRT)	Power	Blood	[Machine failure] Incorrect voltage (Protective)
FC101	Add. error exception, load(ITF)	Power	Blood	CPU failure (Interface)
FC102	Add. error exception, store(ITF)	Power	Blood	CPU failure (Interface)
FC103	Bus error exception, instruction(ITF)	Power	Blood	CPU failure (Interface)
FC104	Bus error exception, data(ITF)	Power	Blood	CPU failure (Interface)
FC105	System call exception(ITF)	Power	Blood	CPU failure (Interface)
FC106	Break point exception (zero division) (ITF)	Power	Blood	CPU failure (Interface)
FC107	Reserve instruction exception (ITF)	Power	Blood	CPU failure (Interface)
FC108	Coprocessor unusable exception (ITF)	Power	Blood	CPU failure (Interface)
FC109	Over flow exception (ITF)	Power	Blood	CPU failure (Interface)
FC110	3PRAM command failure(ITF)	Power	Blood	CPU failure (Interface)
FC111	3PRAM sum failure(ITF)	Power	Blood	CPU failure (Interface)
FC112	PRAM timeout failure(ITF)	Power	Blood	CPU failure (Interface)
FC113	3PRAM ack failure(ITF)	Power	Blood	CPU failure (Interface)
FC114	3PRAM key failure(ITF)	Power	Blood	CPU failure (Interface)
FC115	3PRAM read failure(ITF)	Power	Blood	CPU failure (Interface)
FC116	3PRAM address failure(ITF)	Power	Blood	CPU failure (Interface)
FC117	TASK2 Error(ITF)	Power	Blood	CPU failure (Interface)
FC118	TASK3 Error(ITF)	Power	Blood	CPU failure (Interface)
FC119	TASK4 Error(ITF)	Power	Blood	CPU failure (Interface)
FC120	TASK5 Error(ITF)	Power	Blood	CPU failure (Interface)
FC121	TASK6 Error(ITF)	Power	Blood	CPU failure (Interface)
FC122	TASK7 Error(ITF)	Power	Blood	CPU failure (Interface)
FC123	TASK8 Error(ITF)	Power	Blood	CPU failure (Interface)
FC124	TASK9 Error(ITF)	Power	Blood	CPU failure (Interface)

FC No.	Alarm name	Re-start method	Alarm group	Note
FC125	TASK10 Error(ITF)	Power	Blood	CPU failure (Interface)
FC126	Time Base Error(ITF)	Power	Blood	CPU failure (Interface)
FC136	Failure of CPU test (ITF)	Power	Blood	CPU failure (Interface)
FC137	FRAM write error(ITF)	Power	Blood	Abnormal write to the data memory (Interface)
FC138	Failure of RAM test (ITF)	Power	Blood	Failure of the data memory (Interface)
FC139	Failure of ROM test (ITF)	Power	Blood	Failure of the ROM (Interface)
FC151	Failure of 3PRAM test	Power	Blood	3PRAM failure
FC152	Database [Adjustment data 1] check sum abnormal	Power	Blood	Database of adjustment data 1 is abnormal (Check sum)
FC153	Database [Adjustment data 1] version unmatched	Power	Blood	Database of adjustment data 1 is abnormal (Version)
FC154	Database [Adjustment data 2] check sum abnormal	Power	Blood	Database of adjustment data 2 is abnormal (Check sum)
FC155	Database [Adjustment data 2] version unmatched	Power	Blood	Database of adjustment data 2 is abnormal (Version)
FC156	Database [Adjustment data 3] check sum abnormal	Power	Blood	Database of adjustment data 3 is abnormal (Check sum)
FC157	Database [Adjustment data 3] version unmatched	Power	Blood	Database of adjustment data 3 is abnormal (Version)
FC158	Database [Working data 1] check sum abnormal	Power	Blood	Database of working data 1 is abnormal (Check sum)
FC159	Database [Working data 1] version unmatched	Power	Blood	Database of working data 21is abnormal (Version)
FC160	Database [Working data 2] check sum abnormal	Power	Blood	Database of working data 2 is abnormal (Check sum)
FC161	Database [Working data 2] version unmatched	Power	Blood	Database of working data 2 is abnormal (Version)
FC162	Database [Setting data 1] discrepancy	Power	Blood	Database of setting data 1 is abnormal (Discrepancy)
FC163	Database [Setting data 1] check sum abnormal	Power	Blood	Database of setting data 1 is abnormal (Check sum)
FC164	Database [Setting data 1] version unmatched	Power	Blood	Database of setting data 1 is abnormal (Version)
FC165	Database [Setting data 2] check sum abnormal	Power	Blood	Database of setting data 2 is abnormal (Check sum)

FC No.	Alarm name	Re-start method	Alarm group	Note
FC166	Database [Setting data 2] version unmatched	Power	Blood	Database of setting data 2 is abnormal (Version)
FC167	Database [Treatment data 1] check sum abnormal	Power	Blood	Database of treatment data 1 is abnormal (Check sum)
FC168	Database [Treatment data 1] version unmatched	Power	Blood	Database of treatment data 1 is abnormal (Version)
FC169	Database [Treatment data 2] check sum abnormal	Power	Blood	Database of treatment data 2 is abnormal (Check sum)
FC170	Database [Treatment data 2] version unmatched	Power	Blood	Database of treatment data 2 is abnormal (Version)
FC171	Abnormal check sum of Database[Adjust.data4]	Power	Blood	[Database failure]
FC172	Mismatched Ver. of Databas [Adjust. data4]	Power	Blood	[Database failure]
FC196	Touch key failure	Power	Blood	Touch key turns on more than regulated time.
FC197	Pump power switch failure	Power	Blood	Pump power SW turns on more than regulated time.
FC198	Mute switch failure	Power	Blood	Buzzer mute SW turns on more than regulated time.
FC201	Air detector (Test signal)	Key	Blood	[Sensor abnormality] Abnormal signal was detected by Air Detector in continuous test.
FC202	Air detector (Bubble)	Key	Blood	[Sensor abnormality] Abnormality was detected by Air Detector in continuous test.
FC203	Air detector (Micro Bubble)	Key	Blood	[Sensor abnormality] Abnormality was detected by Air Detector in continuous test.
FC204	Failure of Air detector(AD) test	Key	_	Self test: Abnormality of air detector was detected.
				Colf toots Abroamos life of
FC206	Failure of Conductivity Detector test	Key	_	Self test: Abnormality of conductivity detector was detected.
FC211	Failure of Level Detector(LD 1) test	Key	_	Self test: LD1 detects high level
FC212	Failure of Level Detector(LD 3) test	Key	_	Self test: LD3 detects high level
FC213	Failure of Level Detector(LD 4) test	Key	_	Self test: LD4 detects high level
FC214	Failure of Level Detector(LD 2) test	Key		Self test: LD2 detects high level
FC216	Failure of Fluid detector(FD 1) test	Key	_	Self test: FD1 detects fluid
FC217	Failure of Fluid detector(FD 2) test	Key	_	Self test: FD2 detects fluid

FC No.	Alarm name	Re-start method	Alarm group	Note
FC218	Failure of Fluid detector(FD 3) test	Key	_	Self test: FD3 detects fluid
FC221	Step error 1(No detection of fluid;AD)	Key	Blood	[Step error] Fluid does not reach AD.
FC222	Step error 2(No detection of fluid level; LD1)	Key	Blood	[Step error] Fluid does not reach LD1.
FC223	Step error 3(Fluid level remains high;LD1)	Key	Blood	[Step error] Fluid level does not fall.
FC224	Step error 4(Fluid level remains low;LD2)	Key	Blood	[Step error] Fluid level does not rise.
FC225	Step error 5(No detection of fluid;LD3)	Key	Blood	[Step error] Fluid level does not rise.
FC226	Step error 6(Fluid level remains low;LD4)	Key	Blood	[Step error] Fluid level does not rise.
FC227	Step error 7(Fluid level remains high ;LD2)	Key	Blood	[Step error] Fluid level does not fall.
FC228	Step error 8(Fluid level remains high;LD3)	Key	Blood	[Step error] Fluid level does not fall.
FC229	Step error 9(Fluid level remains high ;LD4)	Key	Blood	[Step error] Fluid level does not fall.
FC301	Press.diff. between 2 Arterial press.sensors	Key	Blood	Abnormality of the machine
FC302	Failure of Arterial press. test (CTR)	Key	_	Abnormality of Arterial pressure sensor P1 in atmosphere
FC303	Failure of Arterial press. test (PRT)	Key	_	Abnormality of Arterial pressure sensor P8 in atmosphere
FC304	Failure of Blood inlet press. test	Key	_	Abnormality of Arterial pressure sensor P2 in atmosphere
FC305	Failure of Plasma press. test	Key	_	Abnormality of Plasma pressure sensor P3 in atmosphere
FC306	Failure of Plasma inlet press. test	Key	_	Abnormality of Plasma inlet pressure sensor P4 in atmosphere
FC307	Failure of Plasma Outlet press. test	Key	_	Abnormality of Plasma outlet pressure sensor P6 in atmosphere
FC308	Failure of Replacement Fluid press. test	Key	_	Abnormality of Plasma replacement pressure sensor P6 in atmosphere
FC309	Failure of Venous press. test failure	Key	_	Abnormality of venous pressure sensor P7 in atmosphere
FC311	Span test error of P2 or P7	Key	Blood	Pressure differs more than 10mmHg between P2 and P7.

FC No.	Alarm name	Re-start method	Alarm group	Note
FC312	Span test error of P3 or P6	Key	Blood	Pressure differs more than 10mmHg between P3 and P6.
FC313	Span test error of P4 or P5	Key	Blood	Pressure differs more than 10mmHg between P4 and P5.
FC401	Offset of Blood detector	Key	Blood	[Sensor failure] Abnormal offset of the Blood Detector
FC411	Rejected on BLD test	Key	Blood	[Sensor abnormality] Failure of the BLD test
FC412	BLD volt. (green/upper)	Key	Blood	[Sensor abnormality] Output of BLD green is abnormal.
FC413	BLD volt. (green/lower)	Key	Blood	[Sensor abnormality] Abnormal output of BLD.
FC414	BLD volt.(red/upper)	Key	Blood	[Sensor abnormality] Abnormal output of BLD.
FC415	BLD volt.(red/lower)	Key	Blood	[Sensor abnormality] Abnormal output of BLD.
FC416	BLD not clear(green)	Key	Blood	[Sensor abnormality] Low output of the BLD.
FC417	BLD not clear(red)	Key	Blood	[Sensor abnormality] Low output of the BLD.
FC422	Failure of Thermistor comparison test(zero)	Key	_	Self test: Machine failure
FC424	Failure of Heater relay test	Key	_	Self test: A heater relay does not work.
FC425	Span test error of TH1 and TH2	Key	Blood	Temperature differs more than 1 degree between TH1 and TH2.
FC426	Abnormal blood warmer temperature	Key	Blood	[Machine failure] Temperature exceeds alarm value.
FC429	Breaking of TH1 wire	Power	Blood	Self test: Machine failure
FC430	Short circuit of TH1 wire	Power	Blood	Self test: Machine failure
FC431	Breaking of TH2 wire	Power	Blood	Self test: Machine failure
FC432	Short circuit of TH2 wire	Power	Blood	Self test: Machine failure
FC501	Failure of BP test	Key	_	Self test: Abnormality in BP operation (normal rotation)

FC No.	Alarm name	Re-start method	Alarm group	Note
FC502	Failure of BP test(reverse)	Key	_	Self test: Abnormality in BP operation (reversal rotation)
FC503	Failure of BP test(stop) (CTR)	Key	_	Self test: Abnormality BP operation (stop from control)
FC504	Failure of BP test(stop) (PRT)	Key	_	Self test: Abnormality BP operation (stop from protection)
FC505	High flow rate (BP)	Key	Blood	[Pump failure] Flow rate exceeds the upper limit.
FC506	Low flow rate (BP)	Key	Blood	[Pump failure] Flow rate exceeds the lower limit.
FC507	Uncontrollable BP	Key	Blood	[Pump failure] Control on BP fails.
FC508	Overload to BP	Key	Blood	[Pump failure] BP is uncontrollable.
FC509	BP reverse rotation	Key	Blood	[Pump failure] BP rotates reversely.
FC511	Failure of PP test	Key	_	Self test: Abnormality in PP operation (normal rotation)
FC512	Failure of PP test(reverse)	Key	_	Self test: Abnormality in PP operation (reversal rotation)
FC513	Failure of PP test(stop) (CTR)	Key	_	Self test: Abnormality in PP operation (stop from control)
FC514	Failure of PP test(stop) (PRT)	Key	_	Self test: Abnormality in PP operation (stop from protection)
FC515	High flow rate (PP)	Key	Blood	[Pump failure] Flow rate exceeds the upper limit.
FC516	Low flow rate (PP)	Key	Blood	[Pump failure] Flow rate exceeds the lower limit.
FC517	Uncontrollable PP	Key	Blood	[Pump failure] Control on PP fails.
FC518	Overload to PP	Key	Blood	[Pump failure] PP is uncontrollable.
FC519	PP reverse rotation	Key	Blood	[Pump failure]
FC521	Failure of RP test	Key	_	Self test: Abnormality in RP operation (normal rotation)

FC	Alarm name	Re-start	Alarm	Note
No.		method	group	Self test: Abnormality in
FC522	Failure of RP test(reverse)	Key	_	RP operation (reversal rotation)
FC523	Failure of RP test(stop) (CTR)	Key	_	Self test: Abnormality in RP operation (stop from control)
FC524	Failure of RP test(stop) (PRT)	Key	_	Self test: Abnormality in RP operation (stop from protection)
FC525	High flow rate (RP)	Key	Blood	[Pump failure] Flow rate exceeds the upper limit.
FC526	High flow rate (RP)	Key	Blood	[Pump failure] Flow rate exceeds the upper limit.
FC527	Uncontrollable RP	Key	Blood	[Pump failure] Control on RP fails.
FC528	Overload to RP	Key	Blood	[Pump failure] RP is uncontrollable.
FC529	RP reverse rotation	Key	Blood	[Pump failure] RP rotates reversely.
FC531	Pump tube uninstalled	Key	Blood	Pump tube is not installed.
FC541	Failure of IP test	Key	_	Self test: Abnormality in IP operation
FC542	Failure of IP test(stop) (CTR)	Key	_	Self test: Abnormality in IP operation (stop by control)
FC543	Failure of IP test(stop) (PRT)	Key	_	Self test: Abnormality in IP operation (stop by protection)
FC544	High flow rate (IP)	Key	Blood	[Pump failure] Flow rate exceeds the upper limit.
FC545	Low flow rate (IP)	Key	Blood	[Pump failure] Flow rate exceeds the lower limit.
FC546	IP reverse movement	Key	Blood	[Pump failure] Infusion pump (IP) moves backward.
EC604	Egilure of \/4 toot/class\	Kovi		V4 connet be elected
FC601	Failure of V1 test(close)	Key	_	V1 cannot be closed
FC602 FC603	Failure of V1 test(open)	Key	_	V1 cannot be opened
FC604	Failure of V2 test(close)  Failure of V2 test(open)	Key	_	V2 cannot be closed V2 cannot be opened
FC604	Failure of V3 test(close)	Key	_	V3 cannot be opened
FC606	Failure of V3 test(close)	Key	_	V3 cannot be closed
FC607	Failure of V4 test(close)	Key	_	V4 cannot be closed
FC608	Failure of V4 test(close)	Key	_	V4 cannot be closed
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FC No.	Alarm name	Re-start method	Alarm group	Note
FC609	Failure of V5 test(close)	Key	_	V5 cannot be closed
FC610	Failure of V5 test(open)	Key	_	V5 cannot be opened
FC611	Failure of V6 test(close)	Key	_	V6 cannot be closed
FC612	Failure of V6 test(open)	Key	_	V6 cannot be opened
FC613	Failure of V7 test(close)	Key	_	V7 cannot be closed
FC614	Failure of V7 test(close) (PRT)	Key	_	V7 cannot be closed (from protection)
FC615	Failure of V7 test(open)	Key	_	V7 cannot be opened
FC616	Failure of V8 test(close)	Key	_	V8 cannot be closed
FC617	Failure of V8 test(close) (PRT)	Key	_	V8 cannot be closed (from protection)
FC618	Failure of V8 test(open)	Key	_	V8 cannot be opened
FC619	Failure of V9 test(close)	Key	_	V9 cannot be closed
FC620	Failure of V9 test(open)	Key	_	V9 cannot be opened
FC621	Failure of V10 test(close)	Key	_	V10 cannot be closed
FC622	Failure of V10 test(open)	Key	_	V10 cannot be opened
FC623	Failure of V11 test(close)	Key	_	V11 cannot be closed
FC624	Failure of V11 test(close) (PRT)	Key	_	V11 cannot be closed (from protection)
FC625	Failure of V11 test(open)	Key	_	V11 cannot be opened
FC626	Failure of V12 test(close)	Key	_	V12 cannot be closed
FC627	Failure of V12 test(close) (PRT)	Key	_	V12 cannot be closed (from protection)
FC628	Failure of V12 test(open)	Key	_	V12 cannot be opened
FC631	valve 1 error	Key	Blood	Valve 1 does not open / close.
FC632	valve 2 error	Key	Blood	Valve 2 does not open / close.
FC633	valve 3 error	Key	Blood	Valve 3 does not open / close.
FC634	valve 4 error	Key	Blood	Valve 4 does not open / close.
FC635	valve 5 error	Key	Blood	Valve 5 does not open / close.
FC636	valve 6 error	Key	Blood	Valve 6 does not open / close.
FC637	valve 7 error	Key	Blood	Valve 7 does not open / close.
FC638	valve 8 error	Key	Blood	Valve 8 does not open / close.
FC639	valve 9 error	Key	Blood	Valve 9 does not open / close.
FC640	valve 10 error	Key	Blood	Valve 10 does not open / close.
FC641	valve 11 error	Key	Blood	Valve 11 does not open / close.

FC No.	Alarm name	Re-start method	Alarm group	Note
FC642	valve 12 error	Key	Blood	Valve 12 does not open / close.
FC701	Leak error 1	Key	Blood	Rinsing (leak test): P6 does not rise. (30sec, 150mmHg)
FC702	Leak error 2	Key	Blood	Rinsing (leak test): P4 rises more than 10mmHg.
FC703	Leak error 3	Key	Blood	Rinsing (leak test): P5 rises more than 10mmHg.
FC705	Leak error 5	Key	Blood	Rinsing (leak test): P5 does not rise. (30sec, 150mmHg)
FC706	Leak error 6	Key	Blood	Rinsing (leak test): Any of P2,P3,P4,P5,P6,P7 doesn't keep the level. (The pressure falls more than 20mmHg)
FC708	Leak error 8	Key	Blood	Rinsing (leak test): P5 does not rise. (30sec, 200mmHg)
FC709	Leak error 9	Key	Blood	Rinsing (leak test): P4 rises more than 10mmHg.
FC710	Leak error 10	Key	Blood	Rinsing (leak test): P6 rises more than 10mmHg.

## 7.7.3 Information (DMxxx)

DM No.	Information Name	Re-start method	Alarm Group	Note
DM001	IP completed	Auto	Inform.	IP infusion completed
DM002	Rinse completed	Auto	Inform.	Rinsing completed
DM003	Priming completed	Auto	Inform.	Priming completed
DM004	Treatment completed	Auto	Inform.	Volume target completed
DM005	Return completed	Auto	Inform.	Return completed
DM006	No syringe	Auto	Inform.	The syringe isn't set.
DM007	IP setting value is 0	Auto	Inform.	IP flow rate isn't set.
DM008	PU temperature rise	Auto	Inform.	Internal of PU temperature rose

### 7. ALARMS

## 8. DATA RECORD FUNCTION OF THE MA-03

The MA-03 has three kinds of data record function which are mentioned below:

- > Alarm history
- > Graph display
- > Data logging

## 8.1 Alarm history

#### 8.1.1 Outline

The history of the alarm occurrence is recorded.

Every alarm is recorded from "Install the tubing" to "Detach the tubing".

When the "Install the tubing" process for next treatment is selected, previous data is cleared.

## 8.1.2 The display method

1. The alarm history can be confirmed by touching the Alarm history/Graph key in the maintenance mode menu.

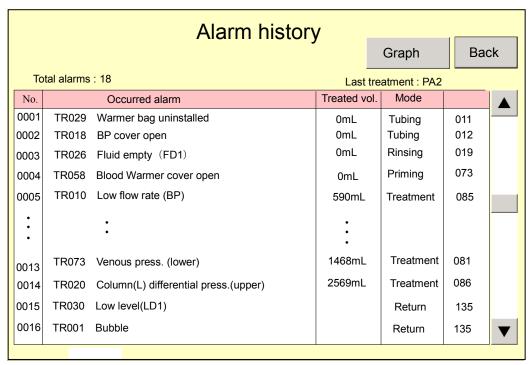


Figure 8.1 Alarm History Screen

2. One screen shows up to 16 alarm histories, and the following data is displayed on the following page. The next / previous page can be seen by touching the scroll bar on the right side of the page.

- 3. Displayed treated volume is:
  - a. Before treatment: 0mL
  - b. During treatment: Treated volume at the time of alarm occurrence
  - c. After treatment: The em dashes
- 4. Displayed process is:
  - a. During the installation of the tubing: "Tubing"
  - b. During rinsing: "Rinsing"
  - c. During priming: "Priming"
  - d. During treatment: "Treatment"
  - e. During return: "Return"
  - f. After return: "Return"

## 8.2 Graph display

#### 8.2.1 Outline

The data of the pressure in the extra corporeal circuit is recorded and displayed by a graph.

The data is recorded from Treatment to Return.

### 8.2.2 The display method of pressure graph

1. Displayed items differ, depending on the treatment. Here is the list of the items.

Treatment method	Displayed items				
PA2	Venous	Arterial	TMP	Separator	Plasma inlet
	press.	press.		press. loss	press.

- 2. Method to display the screen
  - a. During treatment or return process

    If the Check value key is displayed, the graph can be displayed. Touch the Check value key and display the "Check Value" screen. And touch the Graph key.
  - b. During maintenance mode (In this case, last treatment data is displayed)
    Touch the Alarm history/Graph key on the "Mode Menu" screen and display the
    "Alarm History" screen. And touch the Graph key.
- 3. The method to operate the "Graph" screen

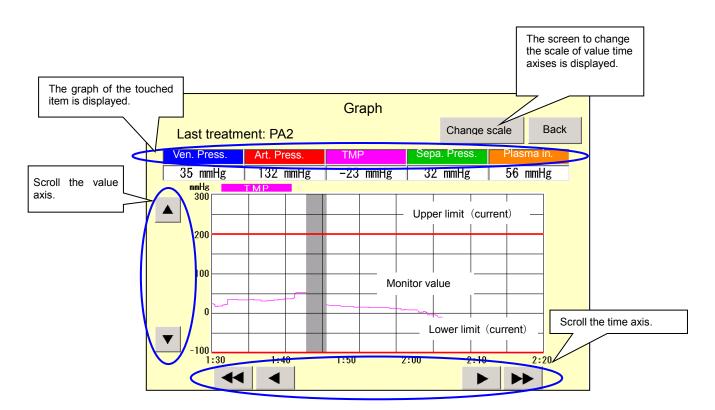


Figure 8.2 Graph Screen (of blood circuit pressure)

## 8.3 Data logging

#### 8.3.1 Outline

The treatment data for every preset volume and alarm data for every alarm occurrence is recorded to a memory card.

It records one file for every treatment data, and the maximum amount is 150 files. The files are overwritten in the recorded order when the amount exceeds 150.

If the memory card is connected to a personal computer, the data can be read and processed with some applications, such as Microsoft Excel.

# **⚠** WARNING

Clinical data logged on the card shall not be used for other purpose than a reference of the physician in charge of the patient.

## 8.3.2 Corresponding card

Compact flash card (Type 1)

1) Memory size 4MB 512MB

2) Format type : FAT163) Drive voltage : 3.3V

# **⚠** CAUTION

A compact flash card formatted on Windows-XP may sometimes not function properly. Format it with other OS than Windows-XP.

A commercially available preformatted CF card is recommended to use.

Insert the card to the data logging unit that is mounted at the rear of the machine.

# **⚠** CAUTION

Confirm the Card IN Lamp of the Data Logging unit is lit when a card is inserted. In case the Card IN Lamp is not lit while a card is inserted, the card may not be properly recognized. Extract the card once and reinsert it.

While the unit is accessing the card, the ACCESS Lamp on the Data Logging unit is lit. Do not remove the card while the lamp is lit, or the card may be damaged. Do not pull it out while lighting.

## 8.3.3 The data classification and items which are recorded

#### 1. Header data

Treatment mode, condition, and status are recorded on the head of a file. Recorded data

PA2
Date (When the tubing is installed)
Patient No. (4-digit number)
Machine name, Serial No., Version
Treatment mode
_
Result of start-up test
Volume target
Treated value
Infused volume (IP)
_
Start Treatment
Return completes
Return volume (in the Separator)
Return volume (out of Separator)
Return volume (after plasma in returned)

#### 2. Treatment data

The treatment data for every volume that was preset by every facility are recorded.

#### Recorded data

recorded data		
Item	PA2	
Time	Clock time and relative time based on the start of installing the tubing.	
Treated volume	Plasma treated volume	
Pump flow rate	Blood pump(BP) flow rate Plasma pump(PP) flow rate, Infusion pump(IP) rate	
Pressure value	Arterial press. Venous press. Blood inlet press. Separator differential press. TMP Column differential press. (left)/(right)	
Other	Blood leak ratio, Temperature Conductivity, BLD voltage	

#### 8. DATA RECORD FUNCTION

#### 3. Alarm history data

Alarm data is recorded every time alarm occurs.

#### Recorded data

PA2
Sequential numbers
Clock time and relative time based on the start of installing the tubing.
The contents of the alarm.
Treated volume.
The process at the time of alarm occurrence.
The step at the time of alarm occurrence
Alarm point (Only for pressure alarm)
The value by which the alarm is generated (Only for pressure alarm)

#### 4. Time at processes switched

Start of Installing the tubing, Rinsing start, Priming completion, Treatment start, Treatment target reached time, Return start, Re-priming start, Re-return start

Recorded data: Clock time and relative time based on the start of installing the tubing.

#### 5. Operation status data

The data shows the condition of operation.

The data is recorded at Treatment start, Return completion, and every preset volume (same as the treatment).

#### Recorded data

PA2		
Clock time and relative time based on the start of installing the tubing		
Treated volume		
Volume target		
Return volume (inside and outside of the separator, after plasma return)		
Re-returning volume		
Arterial pressure alarm (upper/lower)		
Venous pressure alarm (upper/lower)		
Venous pressure (Auto-upper/lower)		
Limit value of Venous pressure alarm (Auto-lower)		
TMP alarm (upper)		
Column differential pressure alarm (upper)		
Temperature target of Blood Warmer		
FD 1 Valid / Invalid		
BLD second calibration Before / After		

#### 6. Information of Rinsing/Priming

PA2	
Rinsing/Priming	Separate/Package
Rinsing volume (B	lood paths of Separator)
Rinsing Volume (C	Columns)
Priming volume (B	lood paths of Separator)
Priming volume (C	columns)

### 8.3.4 The method of operation

- Selection of valid or invalid
   To use the data logging, select the "valid " on the "Facility Data" screen in the maintenance mode. (Selection of Data Logging> Facility data Common Parameter for Facility ).
- 2. Selection of interval to log data

  Select the interval to log data on the "Facility Data" screen in the maintenance mode.

  (Interval to logging data > Facility data Common Parameter for Facility).
- 3. Before using the data logging
  After touching the Confirm key on the "Treatment Mode Selection 3" screen, Selection of "Data Logging" screen is displayed.

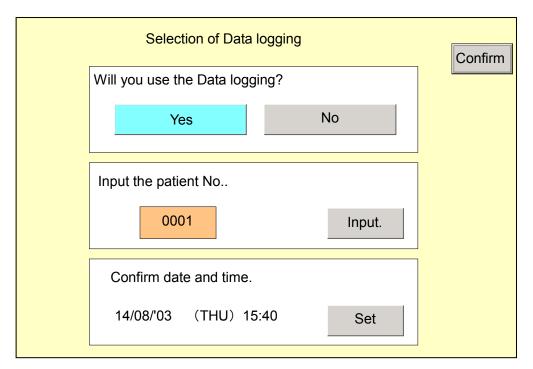


Figure 8.3 Selection of Data Logging Screen

- a. To use Data logging: Select Yes key.
- b. No to use Data logging: Select No key.
- c. Input the patient No. (4-figure number) and touch the Confirm key.



Time is necessary to manage the date file on the card. If the time displayed on the LCD is not correct, touch the Set key and set the time.

#### 8. DATA RECORD FUNCTION

#### 4. After using the data logging

To use the Data logging, touch the Confirm key on the "Treatment is Finished" screen after the treatment is finished.

The "Saving the Data" screen is displayed. The data is recorded on the card from the machine.

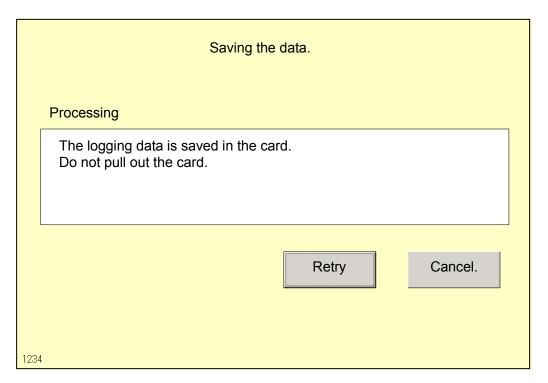


Figure 8.4 Saving the Data Screen

After data logging to the card completes normally, this screen closes automatically.

If the card is not inserted, the message "Please insert the card" appears, and Cancel key is displayed. To cancel the data logging, touch the Cancel key.

If abnormality occurs during the data logging, the Retry key is displayed. To re-save, touch the Retry key.

# 8.3.5 File management

File in the card can be managed in the maintenance mode.

Touch the Logging data management key and Management of the "Logging Data" screen is displayed. (Management of the Logging data > Facility data - Common)

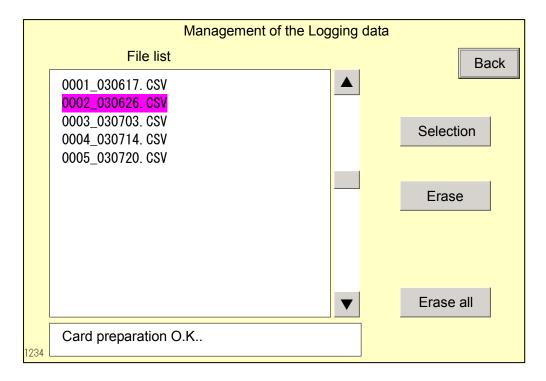


Figure 8.5 Management of the Logging Data Screen

The files in the card are read and file names are displayed on the screen. Select the file name and touch the Selection key. Selected file name is displayed in aqua.

To erase the selected file, touch the Erase key.

If you touch the Erase all key, all files in the card are erased.

# 8. DATA RECORD FUNCTION

# 9. MAINTENANCE AND INSPECTION OF THE MA-03

# **MARNING**

The operating life of the MA-03 and its optimum operating conditions depend much upon regular care, maintenance, and meticulous performance of safety-related inspections.

# **⚠** WARNING

- 1. Before you take care of the MA-03, make sure that the power plug is not connected to the AC power outlet to avoid an electric shock.
- Do not put the accessories in any solution. Prevent fluid from flowing into inside the machine.
- 3. When using the disinfectant, follow the manufacturer's instructions.
- 4. After cleaning, confirm the MA-03 is dry before the Mains plug is connected to the AC power outlet.

# **9.1 Care**

# 9.1.1 Cleaning the Surface



Do not use the solvent (i.e. thinner and benzine) or abrasive cleanser.

They may damage the surface of the MA-03.

Never use undiluted sodium hypochlorite concentrate solution (bleaching agent).

Use of agent containing up to 70% of alcohol is allowed.

Accessories should not be sterilized with autoclave or high-density ozone.



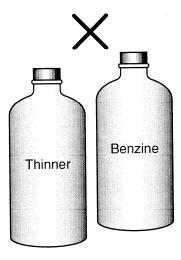
Based on the rules set by medical institutions, cleaning should be conducted with see the following description.

Clean surface with a squeezed soft cloth moistened with a diluted neutral detergent or diluted disinfectant alcohol.

Do not touch the connector assembly and never moisten it.

Care of the unit's exterior should be performed with a MOIST cloth. For surface disinfection, the cloth may be moistened with a diluted sodium hypochlorite solution (max. concentration of 0.5%).





# 9.2 Inspection Before Use



For safe and proper use, inspecting the MA-03 before use has to be done.



At the Beginning of the Day:

Prior to daily use, the following points should be confirmed.

# 9.2.1 Prior to Turning Power On

## External View

- 1. No deformation due to moving.
- 2. The MA-03 should be clean.
- 3. The MA-03 should be dry.
- 4. There should be no damaged part.

# Power Cord

- 1. No heavy object is placed on the power cord.
- 2. There should be no damage to the power cord. (No core reveals. The wire should not come down.)
- 3. The power cord should be connected to the outlet with grounding line.

# 9.2.2 After Turning Power On

### ■ External View

- 1. There should be no smoke or abnormal smell.
- 2. There should be no abnormal sound.

# 9.3 Check during operation and after use for;

- no fluid leakage,
- 2. no smoke nor abnormal smell,
- 3. no abnormal noise, and
- 4. no trace of Blood and/or Rinsing/Priming solution,



When a trace of Blood and/or Rinsing/Priming solution is found, wipe it off to prevent a trouble afterward, according to the instruction provided in "9.1.1Cleaning the Surface" of this Manual.

# 9.4 Maintenance of the System

Safety-related inspection and maintenance of the MA-03 must be carried out only by person authorized by KANEKA PHARMA AMERICA LLC.

For further details on safety-related inspections and maintenance, see the MA-03 Maintenance manual.

When a trace of Blood and/or Rinsing/Priming solution is found, wipe it off to prevent a trouble afterward, according to the instruction provided in "9.1.1 Cleaning the Surface" of this Manual.



Safety-related inspection and maintenance of the system must be carried out in a safe place.

# 10. OPERATION SWITCH-OVER TIMETABLE

START 300 mL Whole Blood Circulation Only				
Treated Plasma (mL)	Adsorption Column (Left)		Adsorption Column (Right)	
0	Adsorption (1)	500 mL	Standby	
500	Plasma Out	Re-Priming Solution 140 mL		
	Regeneration	Regeneration Solution 105 mL	Adsorption (2)	600 mL
	Replacement	Replacement Solution 355 mL		
1,100			Plasma Out	Re-Priming Solution 140 mL
	Adsorption (3)	600 mL	Regeneration	Regeneration Solution 105 mL
			Replacement	Replacement Solution 355 mL
1,700	Plasma Out Regeneration Replacement		Adsorption (4)	
2,300	Adsorption (5)		Plasma Out Regeneration Replacement	
2,900	Plasma Out Regeneration Replacement		Adsorption (6)	
3,500	Adsorption (7)		Plasma Out Regeneration Replacement	
4,100	Plasma Out Regeneration Replacement		Adsorption (8)	
4,700	Adsorption (9)		Plasma Out Regeneration Replacement	
5,300	Plasma Out Regeneration Replacement		Adsorption (10)	
5,900	Adsorption (11)		Plasma Out Regeneration Replacement	
6,500	Plasma Out Regeneration Replacement		Adsorption (12)	

note: In case the TR038 Abnormal conductivity alarm occurs, the value of the Treated Plasma at switching-over columns shifts larger because the machine treats an additional replacement up to maximum 300mL in the regenerating-column process and continues plasma treatment up to maximum 300mL.

# 10. OPERATION SWITCH-OVER TIMETABLE

# 11. PUMP FLOW RATE REGULATION DURING OPERATION & RETURN OF THE MA-03

# 11.1 Restrictive Pressure Limits Affecting Pump Flow Rate

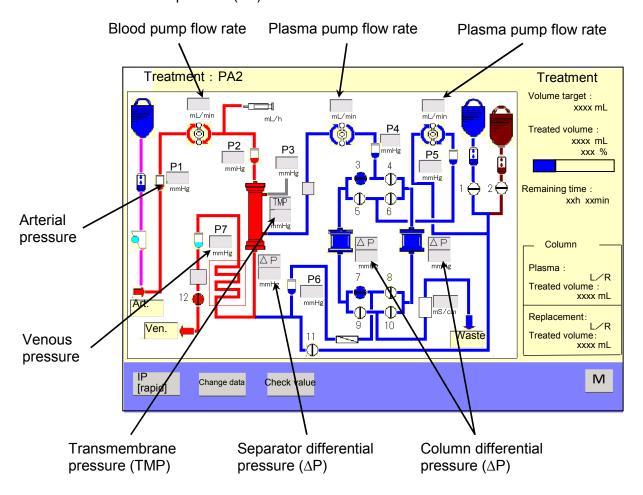
If any of the following conditions occurs, the affected pump will decelerate immediately and continue to decelerate until that condition is corrected (Table 11.1).

Table 11.1. Pump flow rate regulation during operation.

rable 11.1. Fump now rate regulation during operation.			
Pump	ndition		
Blood pump	1. Arterial pressure -150 mmHg (blood flow rate > 20 mL/min.) note: -150 mmHg = -170 mmHg (alarm lower limit) + 20mmHg -70 mmHg (blood flow rate 20 mL /min.) note: This regulation works only in case the pump starts from 0mL/min  2. Venous pressure venous pressure alarm upper limit -20mmHg (set by operator)		
	Separator differential pressure 80 mmHg     note: 80 mmHg = 100 mmHg (alarm upper limit) - 20mmHg		
Plasma pump	<ol> <li>Transmembrane pressure (TMP) 40 mmHg         note: 40 mmHg = 60 mmHg (alarm upper limit) - 20mmHg</li> <li>Column differential pressure 100 mmHg         note: 100 mmHg = 120 mmHg (alarm upper limit) - 20mmHg</li> </ol>		
Replacement pump	Column differential pressure 100 mmHg     note: 100 mmHg = 120 mmHg (alarm upper limit) - 20mmHg		

# 11.2 Restrictive Pressure Display For Pump Flow Rate

- 1. The Blood, plasma and/or replacement pump speeds may decrease from their set value, if the pressure exceeds the upper or lower alarm limit associated with each pump.
- 2. The following indication on the screen will turn to be yellow and blink depending on which restrictive pressure limit are exceeded.
  - · Blood pump flow rate
  - · Plasma pump flow rate
  - · Replacement pump flow rate
  - · Arterial pressure
  - · Venous pressure
  - Separator differential pressure (△P)
  - Transmembrane pressure (TMP)
  - Column differential pressure(∆P)



# 12. EXTRACORPOREAL VOLUMES

Below are the blood and plasma volumes for the LIPOSORBER® LA-15 System:

	Blood	Plasma
Tubing System for Plasmapheresis [NK-M3R(UL)]	105	29
SULFLUX ® KP-05 Plasma Separator	55	75
LIPOSORBER® LDL Adsorption Column (AU)	0	140
Total Extracorporeal Volume (404 mL)	160	244

The plasma volume of the plasma separator is the value that the separator is filled with fluid.

# 12. EXTRACORPOREAL VOLUMES

# 13. TECHNICAL INFORMATION OF THE MA-03

# 13.1 Specifications

Table 13.1 MA-03 Specifications.

Item	Specification
Weight	Approximately 77 kg (170 lbs.)
Storage and transportation temperature	-20 to 60°C

# 13.2 Electrical Conditions

Table 13.2 Power specifications.

Phase	Voltage	Frequency	Current
Single	115 VAC ± 10%	50/60 Hz ± 1Hz	5A

Table 13.3. MA-03 setting ranges.

Table 10.0. Nint 00 detailing ratinged.			
Item	Range		
Extracorporeal circulation volume	Approximately 400 mL (not adjustable)		
Treated plasma volume setting range	0 to 20,000 mL (1 ml increments)		
Whole blood flow rate setting range	7 to 200 mL /min		
Plasma flow rate setting range	0 to 40% of whole blood flow rate. (The minimum working flow rate of the plasma pump is 4 mL /min.)		
Venous pressure alarm setting range (upper limit)	0 to 300 mmHg		
Heparin infusion rate setting range	0.0 to 10.0 ml/h (0.1 mL /h increments)		
Blood warmer temperature setting range	35.0 to 39.0°C (0.1°C increments)		

# 13.3 Required Environmental Conditions

Use the MA-03 only in the following locations and environmental conditions.

## Location

1. Operate the MA-03 under the following conditions:

Ambient temperature:15 to 35°C Relative humidity: 30 to 85% (No condensing)

- 2. Locate the MA-03 in a clean, dry area free of dust and moisture.
- 3. Avoid direct sunlight.
- 4. Place the MA-03 on a level floor and avoid vibration and shock.
- 5. Use only a hospital grade outlet when connecting the MA-03 electrical cord to the wall outlet.

# APPENDIX A Abbreviations and Symbols of the MA-03

# 1. Abbreviations and Symbols

# 1.1 Abbreviations

AC : Alternating Current

AD : Air Detector

BLD : Blood Leak Detector

BP : Blood Pump

BSD : Blood/Saline Detector

CD : Conductivity Detector

DC : Direct Current

DD : Drip Detector

FD : Fluid Detector

IP : Infusion Pump

LD : Level Detector

P : Pressure Transducer

PA : Plasma Adsorption

PA2 : 2 Columns regeneration type Plasma Adsorption.

PH : Blood Warmer(Plate Heater)

PP : Plasma Pump

RP : Replacement Fluid Pump

TMP : Trans-Membrane Pressure

V : Valve

# 1.2 Symbols



Strictly observe the instructions regarding the equipment



Observe the instructions regarding the equipment

IPX1

Protection against dripping water (vertical drip)



Degree of protection against electric shock: Type B Applied part



Date of manufacture



Serial Number



**Alternating Current** 



Protective earth terminal (Grounding)



OFF (Turn off power to KANEKA MA-03)



ON (Turn on power to KANEKA MA-03)



ON (System-start switch)



Recyclable battery



Potential equalization conductor

APHERESIS MACHINE Apheresis Machine

# KANEKA PHARMA AMERICA LLC

546 Fifth Avenue, 21st Floor, New York, NY 10036 TEL: (212) 705-4340  $\,$ 

# TUBING SYSTEM FOR PLASMAPHERESIS

# NK-M3R (U)

Instructions for use in adult and pediatric Focal Segmental Glomerulosclerosis (FSGS)

# FSGS

### **Humanitarian Use Device**

Authorized by Federal (USA) law for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

Caution: Federal law restricts this device to sale by or on the order of a physician.

Carefully review the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" and use only under the direction of a licensed physician with appropriate training.

Manufactured by

NIKKISO CO., LTD

Tokyo, Japan

XX-XXXX-XXX

Printed in Thailand, xx/xxxx

### I. Introduction

The Tubing System for Plasmapheresis (NK-M3R(U)) is one of three disposable device components of the LIPOSORBER® LA-15 System. It is comprised of five tubing sets and a membrane filter.

The technical characteristics of the Tubing System for Plasmapheresis (NK-M3R (U)) are explained in Section III of this instructions for use.

Before using the Tubing System for Plasmapheresis (NK-M3R (U)), carefully review this instructions for use and the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" (hereinafter referred to as "Operator's Manual for FSGS").

### II. Indication

The LIPOSORBER® LA-15 System is indicated for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

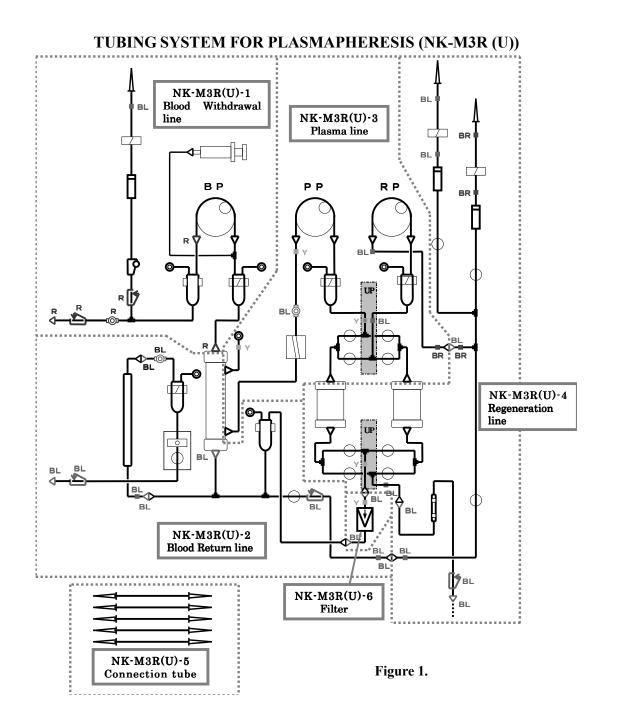
- standard treatment options, including corticosteroids and/or calcineurin inhibitor, treatments are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR)  $\geq$  60 ml/min/1.73 m² or
- The patient is post renal transplantation.

### III. Technical Characteristics

The Tubing System for Plasmapheresis (NK-M3R (U)) consists of the following six packages:

- 1. Blood Withdrawal Line
- 2. Blood Return Line
- 3. Plasma Line
- 4. Regeneration Line
- 5. Connection Tube (5)
- 6. Filter

Diagrams for the complete Tubing System, including each of the five tubing sets and the membrane filter are collectively shown on the following pages.



# 1. BLOOD WITHDRAWAL LINE

Figure 2. NK-M3R(U)-1

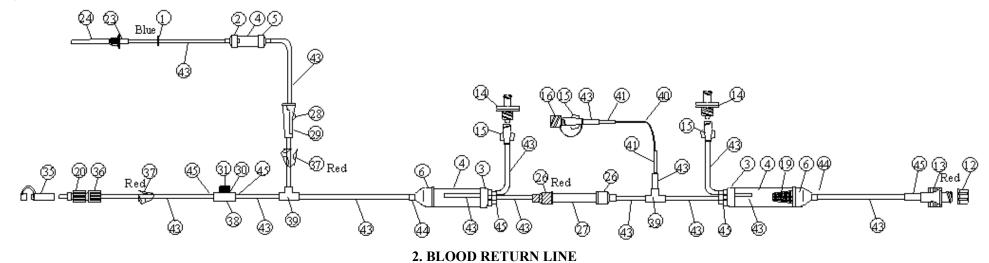
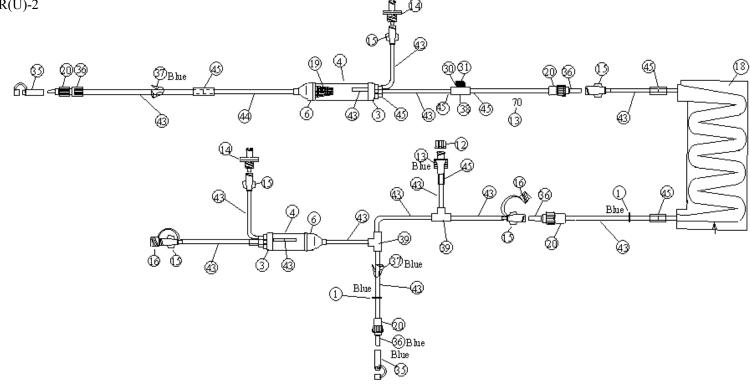
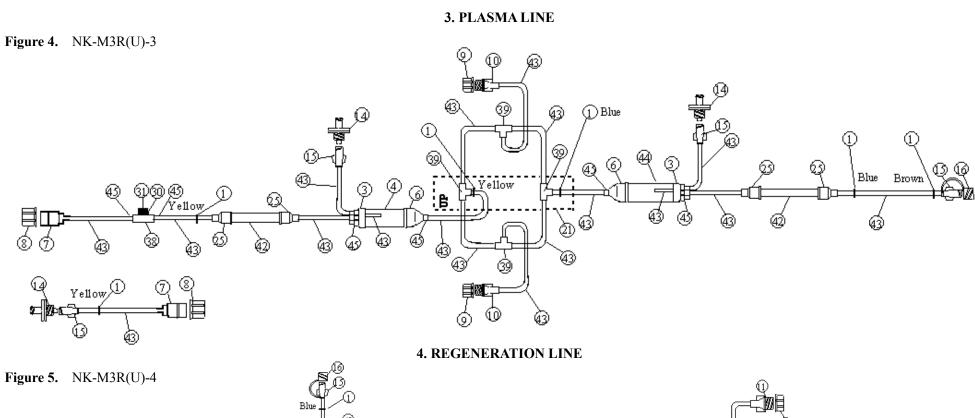
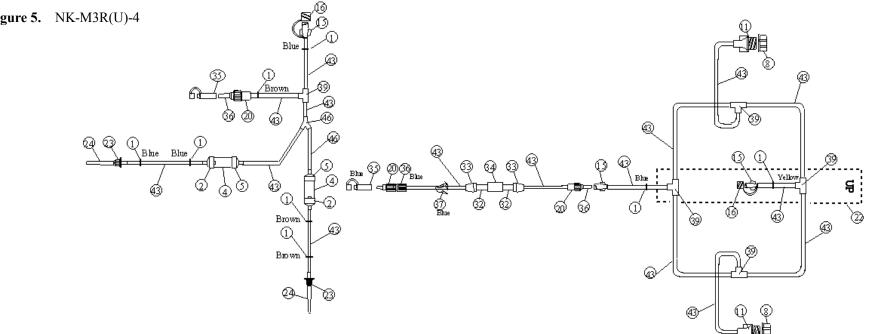


Figure 3. NK-M3R(U)-2



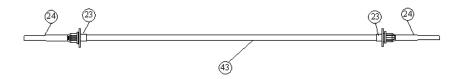
**FSGS** 





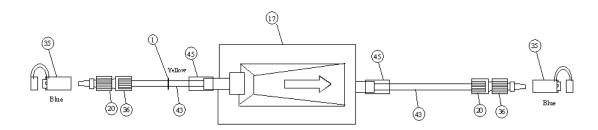
# **5. CONNECTION TUBE (5)**

Figure 6. NK-M3R(U)-5



# 6. FILTER

Figure 7. NK-M3R(U)-6



**List of Component Parts and Materials** 

Part No.	Description	Material(s)
1	Color tube	PVC
2	Chamber cap A	PVC
3	Chamber cap	PVC
4	Chamber tube	PVC
5	Chamber under cap A	PVC
6	Chamber under cap	PVC
7	Coupler connector A	PVC
8	Coupler connector cap A	PP
9	Coupler connector cap B	PP
10	Coupler lock connector A	PC
11	Coupler lock connector B	PC
12	Separator lock connector cap A	PP
13	Separator lock connector D	PVC
14	Transducer protector	PC / Polyester / PTFE
15	Female lock connector	PC
16	Female lock connector cap	PP
17	Membrane filter	PS / Polyester / PTFE / Acrylic resin
18	Heat exchange bag-S	PVC
19	Injection filter D	PP
20	Lock ring-N	PP
21	Panel sheet A	PVC
22	Panel sheet C	PVC
23	Plastic needle	PC

Note: PC Polycarbonate
PVC Polyvinylchloride
PP Polypropylene

PES Polyethersulfone PTFE Polytetrafluoroethylene

## IV. Operations

Carefully review the "Operator's Manual for FSGS" and use only under a physician's direction. **Do not reuse.** 

## V. <u>Contraindications</u>

The LIPOSORBER® LA-15 System must not be used in:

1. patients who have been treated with angiotensin-converting enzyme (ACE) inhibitors within the past 24 hours;

Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER® LA-15 LDL Adsorption Column under concomitant ACE inhibitor medication. The risk of an anaphylactoid reaction may be minimized by withholding the administration of ACE inhibitors for approximately 24 hours before each LDL-apheresis procedure. The time period

Part No.	Description	Material(s)
24	Plastic needle cap	PP
25	Pump connector E	PVC
26	Pump connector G	PVC
27	Pump tube	PVC
28	Roller	PP
29	Roller clamp body	PP
30	Rubber button cap	PP
31	Rubber for needle access port	Isoprene rubber
32	Sensor	ASTM 304
33	Sensor connector A	PC
34	Sensor connector B	PC
35	Shunt connector cap	Polyolefin elastomer
36	Shunt connector	PC
37	Small clamp	PP
38	T-connector for needle access port	PVC
39	T-connector	PVC
40	Tube	PVC
41	Tube	PVC
42	Tube	PVC
43	Tube	PVC
44	Tube	PVC
45	Tube	PVC
46	Y-connector	PVC

to withhold ACE inhibitors should be prolonged, if determined by the treating physician, considering each individual's renal function and the biological half-life of the ACE inhibitor currently in use. If required, ACE inhibitor administration may be resumed on the day of the apheresis treatment but only after the apheresis treatment is complete.

- 2. patients for whom adequate anticoagulation cannot be achieved, such as those with severe hemophilia, severe hemorrhage diathesis, severe gastrointestinal ulcers, or who are receiving vitamin K antagonist medications after surgery;
- 3. patients for whom extracorporeal circulation therapy with the LIPOSORBER® LA-15 System cannot be tolerated such as those with severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, acute apoplexy, or severe uncontrollable hypertension or hypotension; and
- 4. patients with hypersensitivity to dextran sulfate cellulose, heparin or ethylene oxide.

FSGS

### VI. Warnings

- 1. Before using the LIPOSORBER® LA-15 System, including the Tubing System for Plasmapheresis (NK-M3R (U)), carefully review the instructions for use provided for each of the disposables and the Operator's Manual for FSGS. Persons performing the procedures must be qualified to perform extracorporeal procedures, and have completed the required training program. Users should follow all operating or maintenance procedures published by Kaneka Pharma America LLC and use only the disposable device component recommended by Kaneka Pharma America LLC. To do otherwise may result in injury or loss of life.
- 2. The storage and use of this disposable device other than in accordance with the instructions published by Kaneka Pharma America LLC or the use of disposable device components not recommended by Kaneka Pharma America LLC may result in serious patient injury or loss of life. The manufacturer and distributor(s) of this device will not be responsible for patient safety if the procedures to operate and maintain the LIPOSORBER® LA-15 System are other than those specified in this instructions for use and the Operator's Manual for FSGS.
- 3. The LIPOSORBER® LA-15 System may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended to at all times by a physician or qualified health-care professional adequately trained in all aspects of the procedure.
- 4. Rinsing and subsequent priming of the fluid pathway of Tubing System for Plasmapheresis (NK-M3R (U)) with appropriate solutions are necessary before commencing the procedure. Because air bubbles in the Tubing System may lead to complications such as coagulation of plasma and impairment of performance, give full attention to measures that will prevent air bubble migration into the disposables during rinsing and priming.

- 5. To minimize the risk of air embolism, the Blood Return Line must be connected to the air bubble detector.
- 6. During the procedure, all pumps must be stopped prior to opening the roller clamp and tubing pinch clip on the Blood Withdrawal Line and the Blood Return Line. Close the roller clamp and clasp the tubing pinch clip when not in use.
- 7. Citrate preparation (ACD) should never be used as an anticoagulant in the system. The LIPOSORBER® LA-15 System is designed solely for treatment using heparin as an anticoagulant. Anticoagulation is required to prevent thrombus formation from occurring within the extracorporeal circuit. Anticoagulation with too much heparin is associated with an increased risk of bleeding for the patient, especially after the procedure. In order to reduce the risk of bleeding, the puncture sites should be sufficiently compressed so that bleeding is stopped (See Operator's Manual for FSGS at Section 1.7 Notes for Potential Adverse Reactions). In some patients the potential for development of a coagulopathy extending several days post-therapy may exist. In addition to adjusting heparin dosage based on clinical observation during and after the apheresis procedure, Activated Clotting Time and/or partial thromboplastin time (PTT) values may be used (See Operator's Manual for FSGS at Section 1.9.2 Instructions for Use regarding "Determining Heparin Dosage").
- 8. No chemicals or solvents are to be used either inside or outside of this disposable device.
- 9. The Tubing System for Plasmapheresis (NK-M3R (U)) is disposable and is **intended for use in a single procedure only. Never reuse**. Discard this disposable including all unused pieces after each use.

#### VII. Precautions

- 1. Physicians and operators should follow the OSHA and the CDC/ACIP Adult Immunization Guidelines for Hemodialysis Patients. It is recommended that patients be screened for Hepatitis B and other infectious diseases; however due to possible exposure to hepatitis virus, human immunodeficiency virus, and other infectious agents when handling extracorporeal blood circuits, blood or blood products, universal precautions should be taken at all times to prevent the exposure to and transmission of such agents.
- 2. When disposing of the disposable device components and wastes, comply with all local requirements and the policies of the facility regarding precautions for and prevention of infection and environmental pollution.
- 3. All connections of the extracorporeal circuit should be checked carefully prior to initiating and during the procedure. Avoid unnecessary kinking of the tubing lines and the patient's vascular access devices at all times.
- 4. Drip chambers in the extracorporeal circuit should be kept at least <sup>2</sup>/<sub>3</sub> to <sup>3</sup>/<sub>4</sub> full and monitored at all times in order to decrease the risk of air embolism.
- 5. The blood withdrawal lines incorporate an infusion line for I.V. fluids. Each tubing line must be properly connected and cleared of air, prior to the start of Rinse. Do not allow air to be trapped in the set. Puncturing tubing lines may cause air embolism.

- 6. The transducer protectors must be attached and locked to the machine and tubing lines. Strict aseptic technique should be used during this and all procedures. After the completion of the procedure, properly dispose of all used and unused transducer protectors. **Do not reuse**.
- 7. The fluid circuit of this system is intended to be sterile and nonpyrogenic. Aseptic handling techniques are necessary to maintain these conditions. Prior to use, carefully examine the packaging of each tubing set to ensure that it is intact and undamaged. Do not use the Tubing System if the package, sterile bag, protective cap or the product itself is not intact or is damaged. Do not open the bags containing the tubing sets until immediately prior to use.
- 8. In transporting and storing the disposable, handle with care. Store the disposable in a clean and secure area at room temperature (5-30 °C), avoiding exposure to direct sunlight, high humidity or excessive vibration. Handle the Tubing System with care to avoid dropping or other sudden impacts. Do not use a Tubing System that may have been dropped or damaged.
- 9. The expiration date of the Tubing System for Plasmapheresis (NK-M3R (U)) is 2 years from the sterilization date. The Tubing System for Plasmapheresis (NK-M3R (U)) must never be used after the expiration date.



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# **TUBING SYSTEM FOR PLASMAPHERESIS**

# NK-M3R (UL)

Instructions for use in adult and pediatric Focal Segmental Glomerulosclerosis (FSGS)

# FSGS

### **Humanitarian Use Device**

Authorized by Federal (USA) law for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

Caution: Federal law restricts this device to sale by or on the order of a physician.

Carefully review the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" and use only under the direction of a licensed physician with appropriate training.

Manufactured by

NIKKISO CO., LTD

Tokyo, Japan

XX-XXXX-XXX

Printed in Thailand, xx/xxxx

### I. Introduction

The Tubing System for Plasmapheresis (NK-M3R(UL)) is one of three disposable device components of the LIPOSORBER® LA-15 System. It is comprised of five tubing sets and a membrane filter.

The technical characteristics of the Tubing System for Plasmapheresis (NK-M3R (UL)) are explained in Section III of this instructions for use.

Before using the Tubing System for Plasmapheresis (NK-M3R (UL)), carefully review this instructions for use and the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" (hereinafter referred to as "Operator's Manual for FSGS").

### II. Indication

The LIPOSORBER® LA-15 System is indicated for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

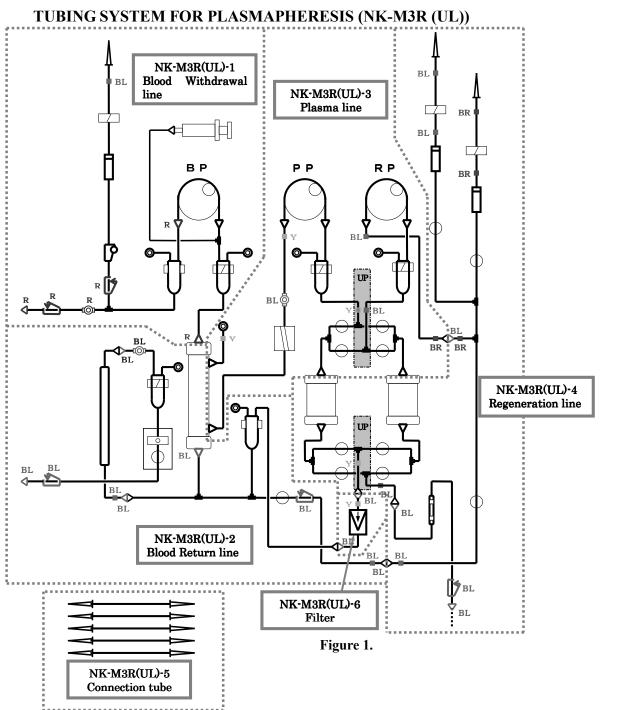
- standard treatment options, including corticosteroids and/or calcineurin inhibitor, treatments are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR)  $\geq$  60 ml/min/1.73 m² or
- The patient is post renal transplantation.

### III. Technical Characteristics

The Tubing System for Plasmapheresis (NK-M3R (UL)) consists of the following six packages:

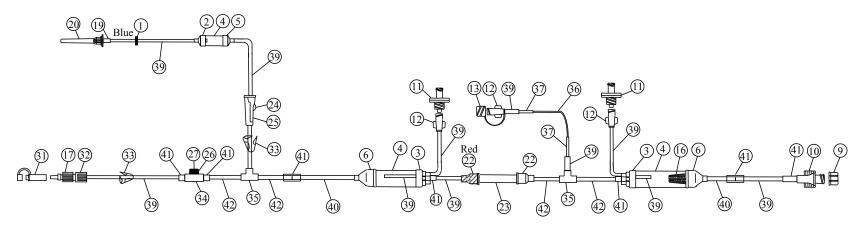
- 1. Blood Withdrawal Line
- 2. Blood Return Line
- 3. Plasma Line
- 4. Regeneration Line
- 5. Connection Tube (5)
- 6. Filter

Diagrams for the complete Tubing System, including each of the five tubing sets and the membrane filter are collectively shown on the following pages.

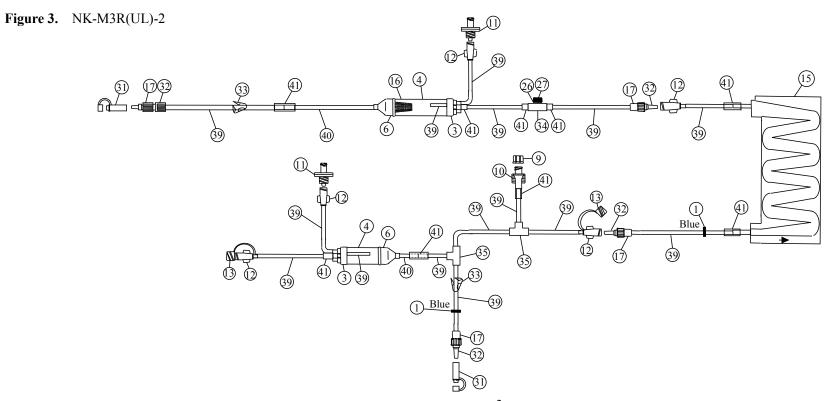


# 1. BLOOD WITHDRAWAL LINE

Figure 2. NK-M3R(UL)-1

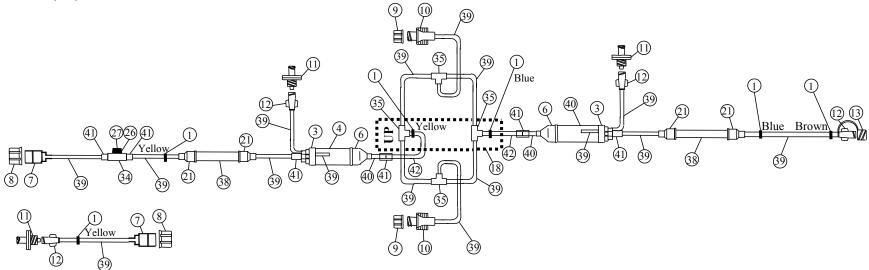


# 2. BLOOD RETURN LINE

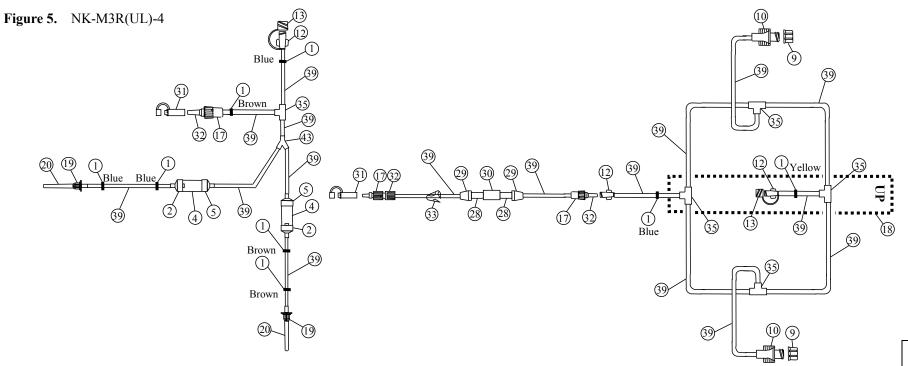


# 3. PLASMA LINE

Figure 4. NK-M3R(UL)-3



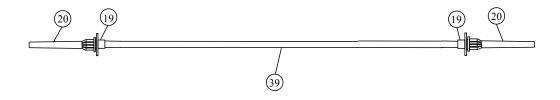
4. REGENERATION LINE



FSGS

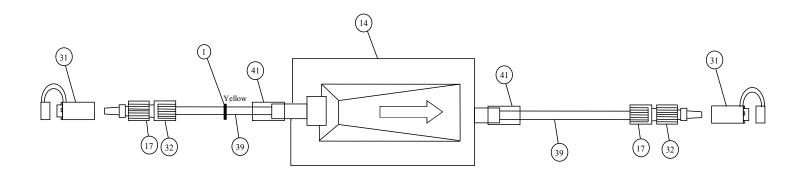
# **5. CONNECTION TUBE (5)**

**Figure 6.** NK-M3R(UL)-5



# 6. FILTER

**Figure 7.** NK-M3R(UL)-6



**List of Component Parts and Materials** 

Part No.	Description	Material(s)	
1	Color tube	PVC	
2	Chamber cap A	PVC	
3	Chamber cap	PVC	
4	Chamber tube	PVC	
5	Chamber under cap A	PVC	
6	Chamber under cap	PVC	
7	Coupler connector A	PVC	
8	Coupler connector cap A	PP	
9	Separator lock connector cap A	PP	
10	Separator lock connector D	PVC	
11	Transducer protector	PC / Polyester / PTFE	
12	Female lock connector	PC	
13	Female lock connector cap	PP	
14	Membrane filter	PS / Polyester / PTFE / Acrylic resin	
15	Heat exchange bag-S	PVC	
16	Injection filter D	PP	
17	Lock ring	PP / PC	
18	Panel sheet E	PVC	
19	Plastic needle	PC	
20	Plastic needle cap	PP	
21	Pump connector E	PVC	
22	Pump connector G	PVC	

Note: PC Polycarbonate
PVC Polyvinylchloride
PP Polypropylene
PES Polyethersulfone
PTFE Polytetrafluoroethylene

IV. Operations

Carefully review the "Operator's Manual for FSGS" and use only under a physician's direction. **Do not reuse.** 

# V. Contraindications

The LIPOSORBER® LA-15 System must not be used in:

1. patients who have been treated with angiotensin-converting enzyme (ACE) inhibitors within the past 24 hours;

Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER® LA-15 LDL Adsorption Column under concomitant ACE inhibitor medication. The risk of an anaphylactoid reaction may be minimized by withholding the administration of ACE inhibitors for approximately 24 hours before each LDL-apheresis procedure. The time period to

Part No.	Description	Material(s)
23	Pump tube	PVC
24	Roller	PP
25	Roller clamp body	PP
26	Rubber button cap	PP
27	Rubber for needle access port	Isoprene rubber
28	Sensor	ASTM 304
29	Sensor connector A	PC
30	Sensor connector B	PC
31	Shunt connector cap	Polyolefin elastomer
32	Shunt connector	PC
33	Small clamp	PP
34	T-connector for needle access port	PVC
35	T-connector	PVC
36	Tube	PVC
37	Tube	PVC
38	Tube	PVC
39	Tube	PVC
40	Tube	PVC
41	Tube	PVC
42	Tube	PVC
43	Y-connector	PVC

withhold ACE inhibitors should be prolonged, if determined by the treating physician, considering each individual's renal function and the biological half-life of the ACE inhibitor currently in use. If required, ACE inhibitor administration may be resumed on the day of the apheresis treatment but only after the apheresis treatment is complete.

- 2. patients for whom adequate anticoagulation cannot be achieved, such as those with severe hemophilia, severe hemorrhage diathesis, severe gastrointestinal ulcers, or who are receiving vitamin K antagonist medications after surgery;
- 3. patients for whom extracorporeal circulation therapy with the LIPOSORBER® LA-15 System cannot be tolerated such as those with severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, acute apoplexy, or severe uncontrollable hypertension or hypotension; and
- 4. patients with hypersensitivity to dextran sulfate cellulose, heparin or ethylene oxide.

# VI. Warnings

- 1. Before using the LIPOSORBER® LA-15 System, including the Tubing System for Plasmapheresis (NK-M3R (UL)), carefully review the instructions for use provided for each of the disposables and the Operator's Manual for FSGS. Persons performing the procedures must be qualified to perform extracorporeal procedures, and have completed the required training program. Users should follow all operating or maintenance procedures published by Kaneka Pharma America LLC and use only the disposable device component recommended by Kaneka Pharma America LLC. To do otherwise may result in injury or loss of life.
- 2. The storage and use of this disposable device other than in accordance with the instructions published by Kaneka Pharma America LLC or the use of disposable device components not recommended by Kaneka Pharma America LLC may result in serious patient injury or loss of life. The manufacturer and distributor(s) of this device will not be responsible for patient safety if the procedures to operate and maintain the LIPOSORBER® LA-15 System are other than those specified in this instructions for use and the Operator's Manual for FSGS.
- 3. The LIPOSORBER® LA-15 System may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended to at all times by a physician or qualified health-care professional adequately trained in all aspects of the procedure.
- 4. Rinsing and subsequent priming of the fluid pathway of Tubing System for Plasmapheresis (NK-M3R (UL)) with appropriate solutions are necessary before commencing the procedure. Because air bubbles in the Tubing System may lead to complications such as coagulation of plasma and impairment of performance, give full attention to measures that will prevent air bubble migration into the disposables during rinsing and priming.

- 5. To minimize the risk of air embolism, the Blood Return Line must be connected to the air bubble detector.
- 6. During the procedure, all pumps must be stopped prior to opening the roller clamp and tubing pinch clip on the Blood Withdrawal Line and the Blood Return Line. Close the roller clamp and clasp the tubing pinch clip when not in use.
- 7. Citrate preparation (ACD) should never be used as an anticoagulant in the system. The LIPOSORBER® LA-15 System is designed solely for treatment using heparin as an anticoagulant. Anticoagulation is required to prevent thrombus formation from occurring within the extracorporeal circuit. Anticoagulation with too much heparin is associated with an increased risk of bleeding for the patient, especially after the procedure. In order to reduce the risk of bleeding, the puncture sites should be sufficiently compressed so that bleeding is stopped (See Operator's Manual for FSGS at Section 1.7 Notes for Potential Adverse Reactions). In some patients the potential for development of a coagulopathy extending several days post-therapy may exist. In addition to adjusting heparin dosage based on clinical observation during and after the apheresis procedure, Activated Clotting Time and/or partial thromboplastin time (PTT) values may be used (See Operator's Manual for FSGS at Section 1.9.2 Instructions for Use regarding "Determining Heparin Dosage").
- 8. No chemicals or solvents are to be used either inside or outside of this disposable device.
- 9. The Tubing System for Plasmapheresis (NK-M3R (UL)) is disposable and is **intended for use in a single procedure only**. **Never reuse**. Discard this disposable including all unused pieces after each use.

# VII. Precautions

- 1. Physicians and operators should follow the OSHA and the CDC/ACIP Adult Immunization Guidelines for Hemodialysis Patients. It is recommended that patients be screened for Hepatitis B and other infectious diseases; however due to possible exposure to hepatitis virus, human immunodeficiency virus, and other infectious agents when handling extracorporeal blood circuits, blood or blood products, universal precautions should be taken at all times to prevent the exposure to and transmission of such agents.
- 2. When disposing of the disposable device components and wastes, comply with all local requirements and the policies of the facility regarding precautions for and prevention of infection and environmental pollution.
- 3. All connections of the extracorporeal circuit should be checked carefully prior to initiating and during the procedure. Avoid unnecessary kinking of the tubing lines and the patient's vascular access devices at all times.
- 4. Drip chambers in the extracorporeal circuit should be kept at least <sup>2</sup>/<sub>3</sub> to <sup>3</sup>/<sub>4</sub> full and monitored at all times in order to decrease the risk of air embolism.
- 5. The blood withdrawal lines incorporate an infusion line for I.V. fluids. Each tubing line must be properly connected and cleared of air, prior to the start of Rinse. Do not allow air to be trapped in the set. Puncturing tubing lines may cause air embolism.

- 6. The transducer protectors must be attached and locked to the machine and tubing lines. Strict aseptic technique should be used during this and all procedures. After the completion of the procedure, properly dispose of all used and unused transducer protectors. **Do not reuse**.
- 7. The fluid circuit of this system is intended to be sterile and nonpyrogenic. Aseptic handling techniques are necessary to maintain these conditions. Prior to use, carefully examine the packaging of each tubing set to ensure that it is intact and undamaged. Do not use the Tubing System if the package, sterile bag, protective cap or the product itself is not intact or is damaged. Do not open the bags containing the tubing sets until immediately prior to use.
- 8. In transporting and storing the disposable, handle with care. Store the disposable in a clean and secure area at room temperature (5-30 °C), avoiding exposure to direct sunlight, high humidity or excessive vibration. Handle the Tubing System with care to avoid dropping or other sudden impacts. Do not use a Tubing System that may have been dropped or damaged.
- 9. The expiration date of the Tubing System for Plasmapheresis (NK-M3R (UL)) is 2 years from the sterilization date. The Tubing System for Plasmapheresis (NK-M3R (UL)) must never be used after the expiration date.



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# SULFLUX® KP-05 PLASMA SEPARATOR

Prior to use, carefully review the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" in its entirety and follow all directions, procedures, and instructions therein. Use only under the direction of a licensed physician with appropriate training.

# **SULFLUX®**

# PLASMA SEPARATOR KP-05

Instructions for use in adult and pediatric focal segmental glomerulosclerosis (FSGS)

# FSGS

# **Humanitarian Use Device**

Authorized by Federal (USA) law for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

Caution: Federal law restricts this device to sale by or on the order of a physician.

Distributed by

# Kaneka Pharma America LLC

546 Fifth Avenue, 21st Floor, New York, NY 10036

Manufactured by

# ASAHI KAŚEI MEDICAL MT CORP.

2111-2 Oaza Sato, Oita-shi, Oita 870-0396, Japan

Instructions for use in Functional Hypercholesterolemia start from the back cover

# I. Introduction

The SULFLUX® KP-05 Plasma Separator is one of three disposable device components of the LIPOSORBER® LA-15 System.

The technical characteristics of the SULFLUX® KP-05 Plasma Separator are explained in Section III of this instructions for use.

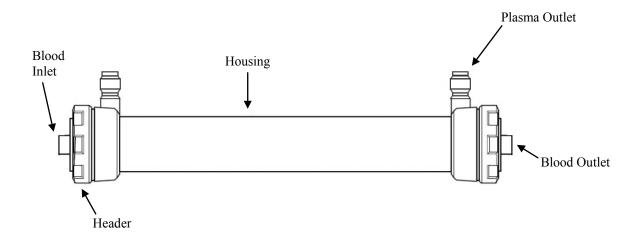
Before using the SULFLUX® KP-05 Plasma Separator, carefully review this instructions for use and the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" (hereinafter referred to as "Operator's Manual for FSGS").

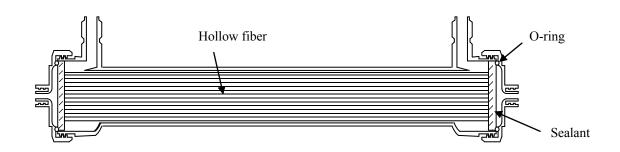
# II. Indication

The LIPOSORBER $^{\$}$  LA-15 System is indicated for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary FSGS when:

- standard treatment options, including corticosteroids and/or calcineurin inhibitor, treatments are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

# **III. Technical Characteristics**





	material	polyethylene (coated with ethylene vinyl alcohol copolymer) 330 μ m	
Hollow Fiber	membrane thickness	50 μ m	
	effective surface area	0.5 m <sup>2</sup>	
	pore size	0.3 μ m	
Housing	material	polycarbonate	
Tiousing	size	34 mmФ x 290 mm	
Sealant	material	polyurethane	
Priming Volume	blood side	55 ml	
Filling volume	plasma side	75 ml	
Filling Liquid	composition	Saline solution	
Sterilization Method	methodology	$\gamma$ -ray irradiation (25 kGy)	

# IV. Performance Characteristics

Sieving Coefficients of Plasma Components were obtained In vivo from a clinical investigation (N=63).

	Sieving Coefficient		
Plasma Component	Mean	S.D.	
Total Protein	1.00	0.02	
Albumin	1.02	0.04	
IgA	1.00	0.06	
lgG	1.00	0.05	
IgM	1.01	0.09	
Total Cholesterol	1.03	0.14	
Triglycerides	1.04	0.12	

# V. Operations

Carefully review and follow the "Operator's Manual for FSGS" and use only under a licensed physician's direction. **Do** not reuse

# VI. Contraindications

The LIPOSORBER® LA-15 System must not be used in:

- 1. patients who have been treated with angiotensin-converting enzyme (ACE) inhibitors within the past 24 hours;
  - Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER <sup>®</sup> LA-15 LDL Adsorption Column under concomitant ACE inhibitor medication. The risk of an anaphylactoid reaction may be minimized by withholding the administration of ACE inhibitors for approximately 24 hours before each LDL-apheresis procedure. The time period to withhold ACE inhibitors should be prolonged, if determined by the treating physician, considering each individual's renal function and the biological half-life of the ACE inhibitor currently in use. If required, ACE inhibitor administration may be resumed on the day of the apheresis treatment but only after the apheresis treatment is complete.
- patients for whom adequate anticoagulation cannot be achieved, such as those with severe hemophilia, severe hemorrhage diathesis, severe gastrointestinal ulcers, or who are receiving vitamin K antagonist medications after surgery;
- 3. patients for whom extracorporeal circulation therapy with LIPOSORBER® LA-15 System cannot be tolerated such as those with severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, acute apoplexy, or severe uncontrollable hypertension or hypotension; and
- 4. patients with hypersensitivity to dextran sulfate cellulose, heparin or ethylene oxide.

# VII. Warnings

- 1. Before using the LIPOSORBER® LA-15 System, including the SULFLUX® KP-05 Plasma Separator, carefully review the instructions for use provided for each of the disposables and the "Operator's Manual for FSGS". Persons performing the procedures must be qualified to perform extracorporeal procedures, and have completed the required training program. Users should follow all operating or maintenance procedures published by Kaneka Pharma America LLC and use only the disposable device components recommended by Kaneka Pharma America LLC. Failure to do so may result in serious injury or loss of life.
- 2. The storage and use of this disposable device other than in accordance with the instructions published by Kaneka Pharma America LLC or the use of disposable device components not recommended by Kaneka Pharma America LLC may result in serious patient injury or loss of life. The manufacturer and distributor(s) of this device will not be responsible for patient safety if the procedures to operate and maintain the LIPOSORBER® LA-15 System are other than those specified in this instructions for use and the "Operator's Manual for FSGS".
- 3. The LIPOSORBER® LA-15 System may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended to at all times by a physician or qualified health-care professional adequately trained in all aspects of the procedure.
- 4. Prior to use of the SULFLUX® KP-05 Plasma Separator, the Plasma Separator must be rinsed with 1000mL of 0.9% Sodium Chloride Injection (USP) and subsequently primed with 500mL of heparinized Lactated Ringer's Injection (USP) pursuant to the automated rinsing and priming process conducted by the LA-15 System. This procedure must be completed for every Plasma Separator prior to use. Because air bubbles in the Plasma Separator may lead to complications such as coagulation of blood and impairment of performance, the operator must ensure that there is no air bubble migration into the Plasma Separator during rinsing and priming.
- 5. SULFLUX® KP-05 Plasma Separator is capable of efficient separation of plasma from the blood flow from 70 to 130 mL/min when the plasma filtrate ratio (plasma flow rate / blood flow rate) is not more than 30%.
- 6. While operating, the transmembrane pressure (TMP) of the SULFLUX® KP-05 Plasma Separator must be under 60 mmHg. If the TMP rises above 45 mmHg, the plasma pump will decelerate until the TMP falls below 45 mmHg. If the TMP reaches or exceeds 65 mmHg for a duration of three seconds or more, the plasma pump will cease operation.
- 7. Citrate preparation (ACD) should never be used as an anticoagulant in the system. The LIPOSORBER® LA15 System is designed solely for treatment using heparin as an anticoagulant. Anticoagulation is required to prevent thrombus formation from occurring within the extracorporeal circuit. Anticoagulation with too much heparin is associated with an increased risk of bleeding for the patient, especially after the procedure. In order to reduce the risk of bleeding, the puncture sites should be sufficiently compressed so that bleeding is stopped (See Operator's Manual for FSGS at Section 1.7 Notes for Potential Adverse Reactions). In some patients the potential for development of a coagulopathy extending several days post-therapy may exist. In addition to adjusting heparin dosage based on clinical observation during and after the apheresis procedure, Activated Clotting Time and/or partial thromboplastin time (PTT) values may be used (See Operator's Manual at Section 1.9.2 Instructions for Use regarding "Determining Heparin Dosage").
- 8. No chemicals or solvents are to be used either inside or outside of this disposable device.
- The SULFLUX® KP-05 Plasma Separator is disposable and is intended for use in a single procedure only.
   Never reuse. Discard this disposable after each use.

# VIII. Precautions

- 1. Physicians and operators should follow the OSHA and the CDC/ACIP Adult Immunization Guidelines for Hemodialysis Patients. It is recommended that patients be screened for Hepatitis B and other infectious diseases, however, due to possible exposure to hepatitis virus, human immunodeficiency virus, and other infectious agents when handling extracorporeal blood circuits, blood or blood products, universal precautions should be taken at all times to prevent the exposure to and transmission of such agents.
- 2. When disposing of the disposable device components and wastes, comply with all local requirements and the policies of the facility regarding precautions for and prevention of infection and environmental pollution.
- 3. All connections of the extracorporeal circuit should be checked carefully prior to initiating and during the procedure. Avoid unnecessary kinking of the tubing lines and the patient's vascular access devices at all times.
- 4. Drip chambers in the extracorporeal circuit should be kept at least 2/3 to 3/4 full and monitored at all times in order to decrease the risk of air embolism.
- 5. The fluid circuit of this system is intended to be sterile and nonpyrogenic. Aseptic handling techniques are necessary to maintain these conditions. Prior to use, carefully examine the packaging of the Plasma Separator to ensure that it is intact and undamaged. Do not use the Plasma Separator if the package, sterile bag, protective cap or the product itself is not intact or is damaged. Do not open the bag containing the Plasma Separator until immediately prior to use.
- 6. In transporting and storing the Plasma Separator, handle with care. Store the Plasma Separator in a clean and secure area at room temperature (0-30°C), avoiding exposure to direct sunlight, high humidity or excessive vibration. Handle the SULFLUX® KP-05 Plasma Separator with care to avoid dropping or other sudden impacts and never allow it to freeze. Do not use a Plasma Separator that may have been dropped, damaged or frozen.
- 7. The expiration date of the SULFLUX® KP-05 is 3 years from the sterilization date. The Plasma Separator must never be used after the expiration date.

# **Humanitarian Use Device**

Authorized by Federal (USA) law for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

Caution: Federal law restricts this device to sale by or on the order of a physician.

**Note:** This product has also been approved by PMA for certain patients with familial hypercholesterolemia.

Carefully review the enclosed Instructions for Use for LIPOSORBER® LA-15 LDL Adsorption Columns and the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" when using this product for the Humanitarian Use indications.

S206L-X

Fig1. HDE label for LIPOSORBER® LA-15 ADSORPTION COLUMN

## **Humanitarian Use Device**

Authorized by Federal (USA) law for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

Caution: Federal law restricts this device to sale by or on the order of a physician.

**Note:** This product has also been approved by PMA for certain patients with familial hypercholesterolemia.

Carefully review the enclosed Instructions for Use for Tubing System for Plasmapheresis NK-M3R(U) and the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" when using this product for the Humanitarian Use indications.

S206L3-X

Fig2. HDE label for Tubing System for Plasmapheresis NK-M3R(U)

### **Humanitarian Use Device**

Authorized by Federal (USA) law for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

**Caution:** Federal law restricts this device to sale by or on the order of a physician.

**Note:** This product has also been approved by PMA for certain patients with familial hypercholesterolemia.

Carefully review the enclosed Instructions for Use for SULFLUX® KP-05 Plasma Separator and the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" when using this product for the Humanitarian Use indications.

S206L2-X

Fig3. HDE label for SULFLUX® KP-05 Plasma Separator

# **Humanitarian Use Device**

Authorized by Federal (USA) law for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

Caution: Federal law restricts this device to sale by or on the order of a physician.

**Note:** This product has also been approved by PMA for certain patients with familial hypercholesterolemia.

Carefully review the enclosed Instructions for Use for Tubing System for Plasmapheresis NK-M3R(UL) and the "LIPOSORBER® LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" when using this product for the Humanitarian Use indications.

S206L3-X

Fig1. HDE label for Tubing System for Plasmapheresis NK-M3R(UL)