TUBING SYSTEM FOR PLASMAPHERESIS

NK-M3R (UL)

Instructions for use in Familial Hypercholesterolemia (FH)

FH

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" and use only under the direction of a licensed physician with appropriate training.

Manufactured by
NIKKISO CO., LTD.
Tokyo, Japan

xx-xxxx-xxxx
Printed in Thailand, 03/2022

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".

II. Indication

The LIPOSORBER® LA-15 System is indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has been either ineffective or not tolerated:

Group A Clinically diagnosed Familial Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dL;

Group B Clinically diagnosed Familial Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dL;

Group C Clinically diagnosed Familial Hypercholesterolemic Heterozygotes with LDL-C ≥ 100 mg/dL and either documented coronary artery disease or documented peripheral artery disease; and

Group D Clinically diagnosed Familial Hypercholesterolemic Heterozygotes with LDL-C ≥ 100 mg/dL, lipoprotein(a) [Lp(a)] ≥ 60 mg/dL and either documented coronary artery disease or documented peripheral artery disease.

The LDL-C levels for the indicated patient populations are baseline LDL-C levels obtained after the patient has had a trial of diet and maximum tolerated combination drug therapy to reduce LDL-C according to the current professional guidelines on the management of blood cholesterol.

Documented coronary artery disease (CAD) includes CAD diagnosed by invasive or computed tomography (CT) coronary angiography, or by electron beam (ultrafast) CT (EBCT), or documented by a history of myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery.

Documented peripheral artery disease (PAD) includes PAD diagnosed by symptoms and/or physical exam (e.g., using the Rutherford classification), ankle-brachial index (ABI), ultrasound exam, pulse volume recording (PVR), or peripheral vascular angiography, or documented by a history of peripheral vascular intervention, peripheral vascular bypass surgery, or minor or major amputation.

Baseline lipid levels are to be determined after stabilization on diet and drug therapy by making two measurements during a 2- to 4-week period. (Note: The two values should be within 10% of each other, indicating a stable condition.)

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.

IV. Operations

Carefully review the "LIPOSORBER® LA-15 System Operator's Manual" and use only under a physician's direction. **Do not reuse.**

TUBING SYSTEM FOR PLASMAPHERESIS (NK-M3R (UL))

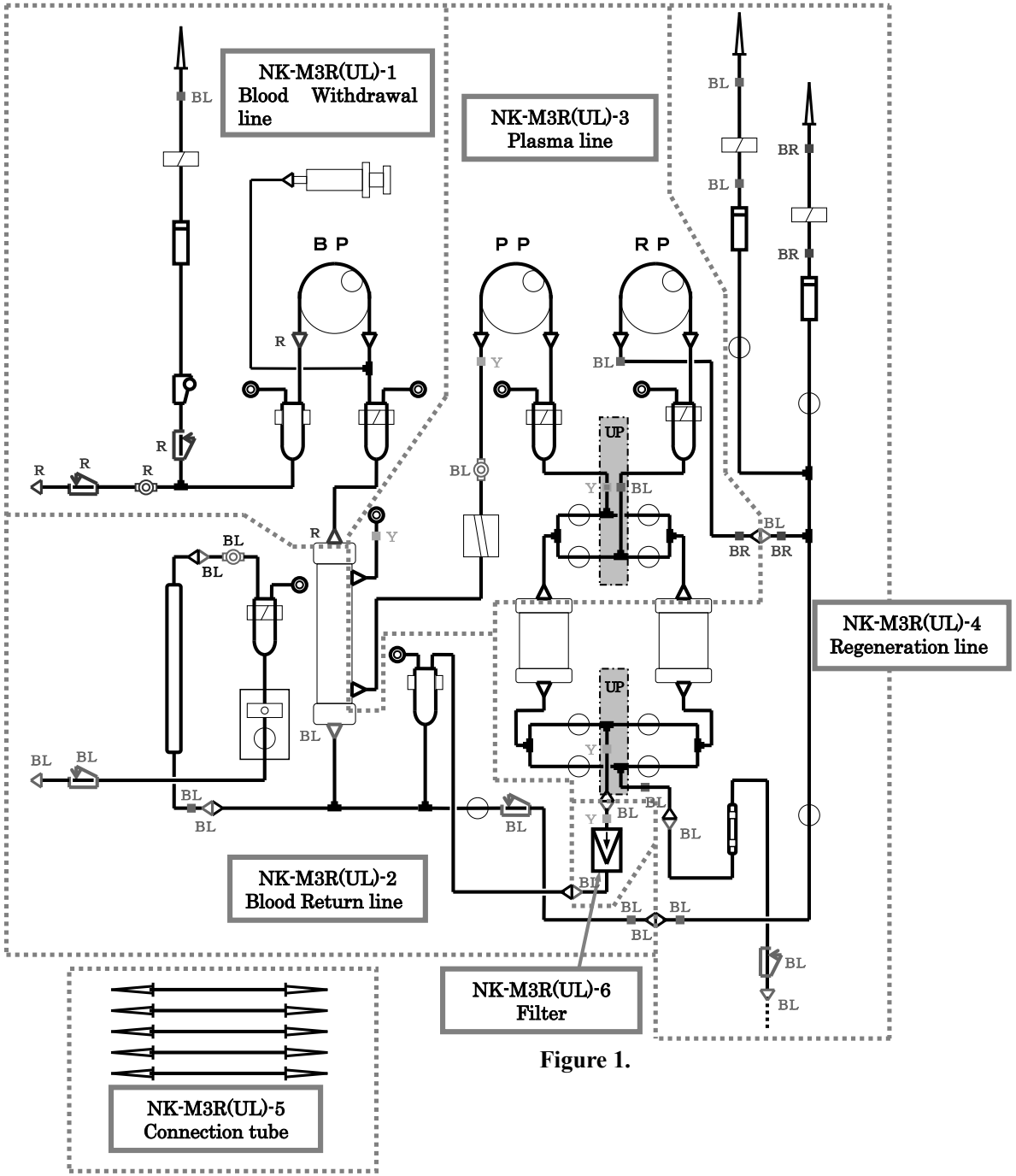
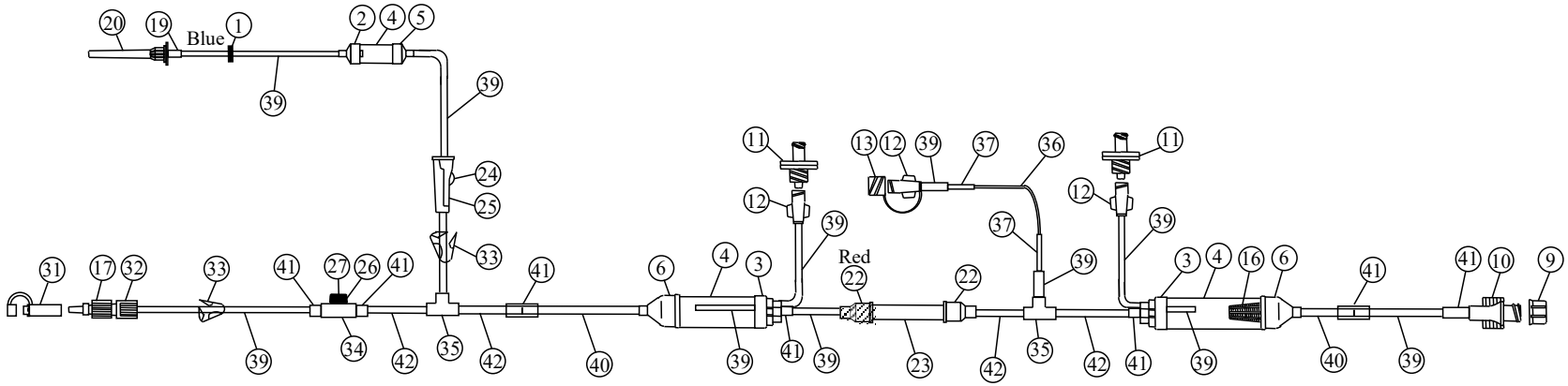


Figure 1.

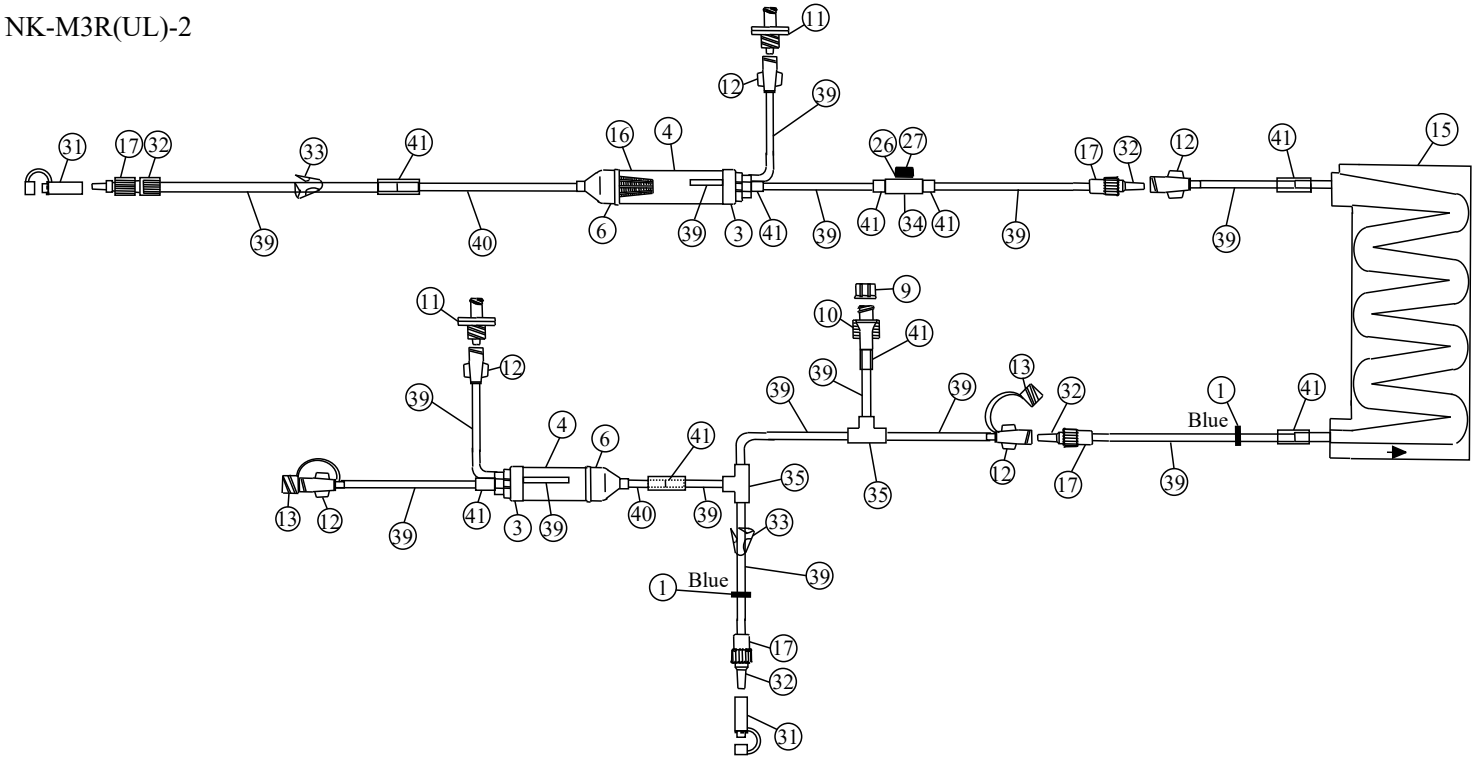
1. BLOOD WITHDRAWAL LINE

Figure 2. NK-M3R(UL)-1



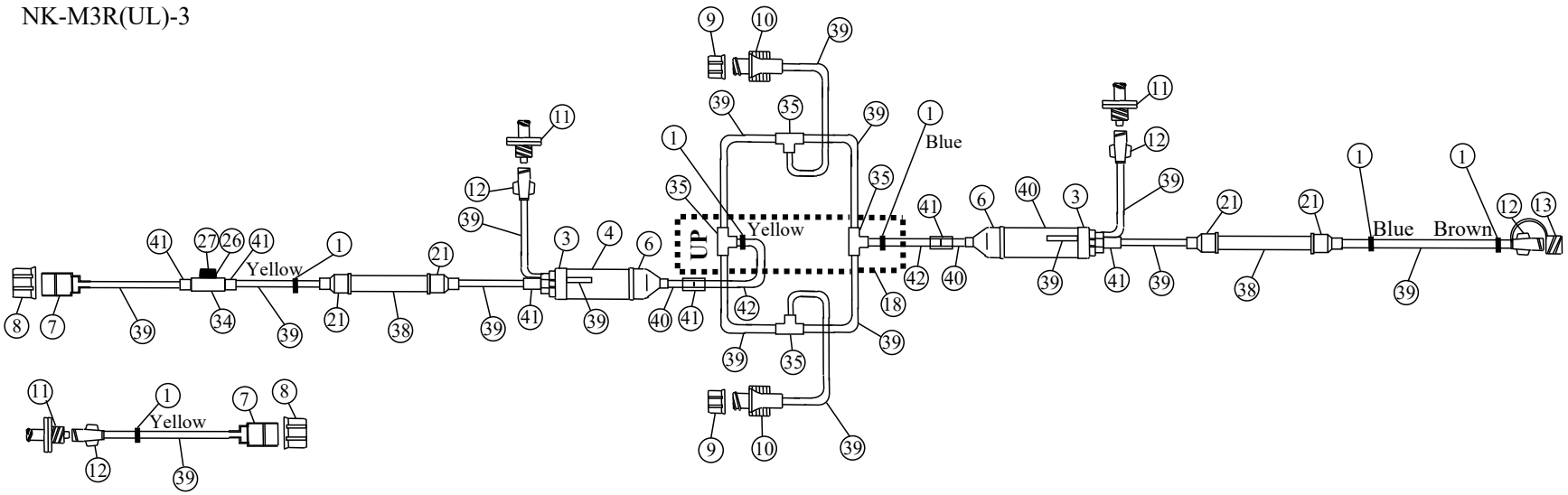
2. BLOOD RETURN LINE

Figure 3. NK-M3R(UL)-2



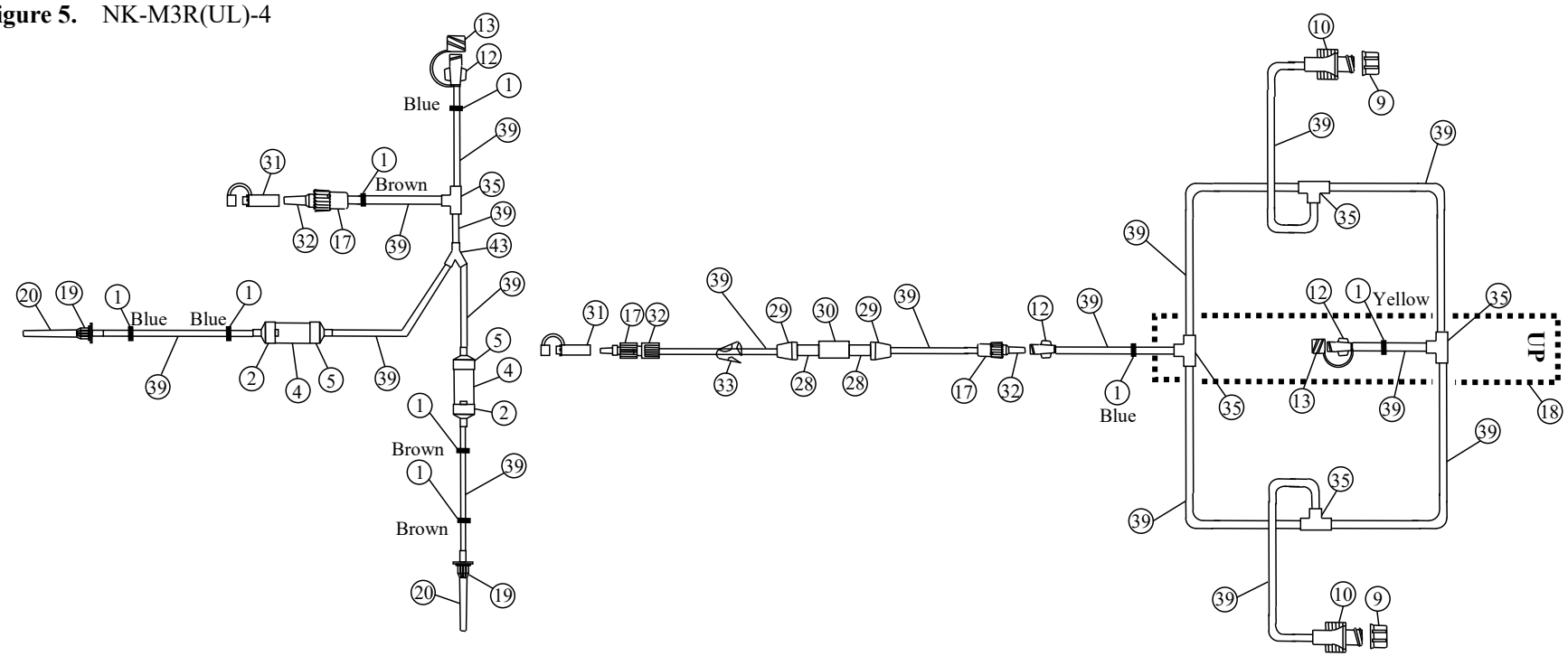
3. PLASMA LINE

Figure 4. NK-M3R(UL)-3



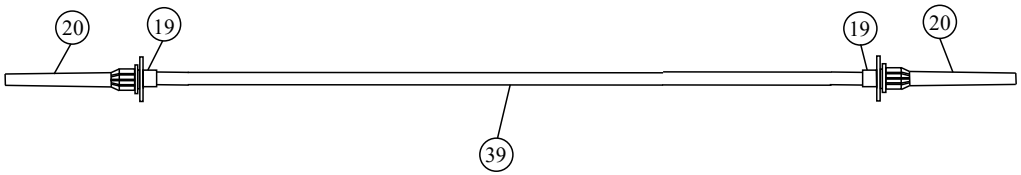
4. REGENERATION LINE

Figure 5. NK-M3R(UL)-4



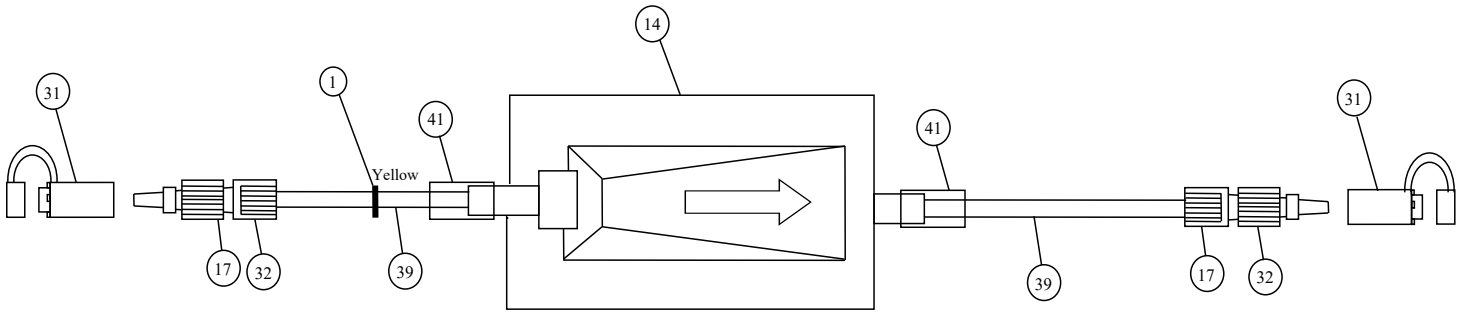
5. CONNECTION TUBE (5)

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	PES / 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
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

Note:
PC Polycarbonate
PVC Polyvinylchloride
PP Polypropylene
PES Polyethersulfone
PTFE Polytetrafluoroethylene

V. Contraindications

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

1. patients who are being treated with angiotensin-converting enzyme (ACE) inhibitors;

   Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER® LA-15 LDL Adsorption Column under concomitant ACE inhibitor medication. Temporal ceasing of ACE inhibitor intake to remove its bioactivity from the patient's blood may not always be sufficient to avoid such adverse reactions. The ACE inhibitors should be switched to another antihypertensive medication (for example, angiotensin II receptor blockers (ARBs)) at the medical discretion of the treating physician.

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 "LIPOSORBER® LA-15 System 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 Medical America LLC and use only the disposable device component recommended by Kaneka Medical 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 Medical America LLC or the use of disposable device components not recommended by Kaneka Medical 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.

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 at Section **1.6. 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 at Section **1.8.3 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 procedure.

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 policy 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 ⅔ to ¾ 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 ºC), 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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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 m^2 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-xxxx
Printed in Thailand, 03/2022

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) ≥ 60 mL/min/1.73 m^2 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.

IV. Operations

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

TUBING SYSTEM FOR PLASMAPHERESIS (NK-M3R (UL))

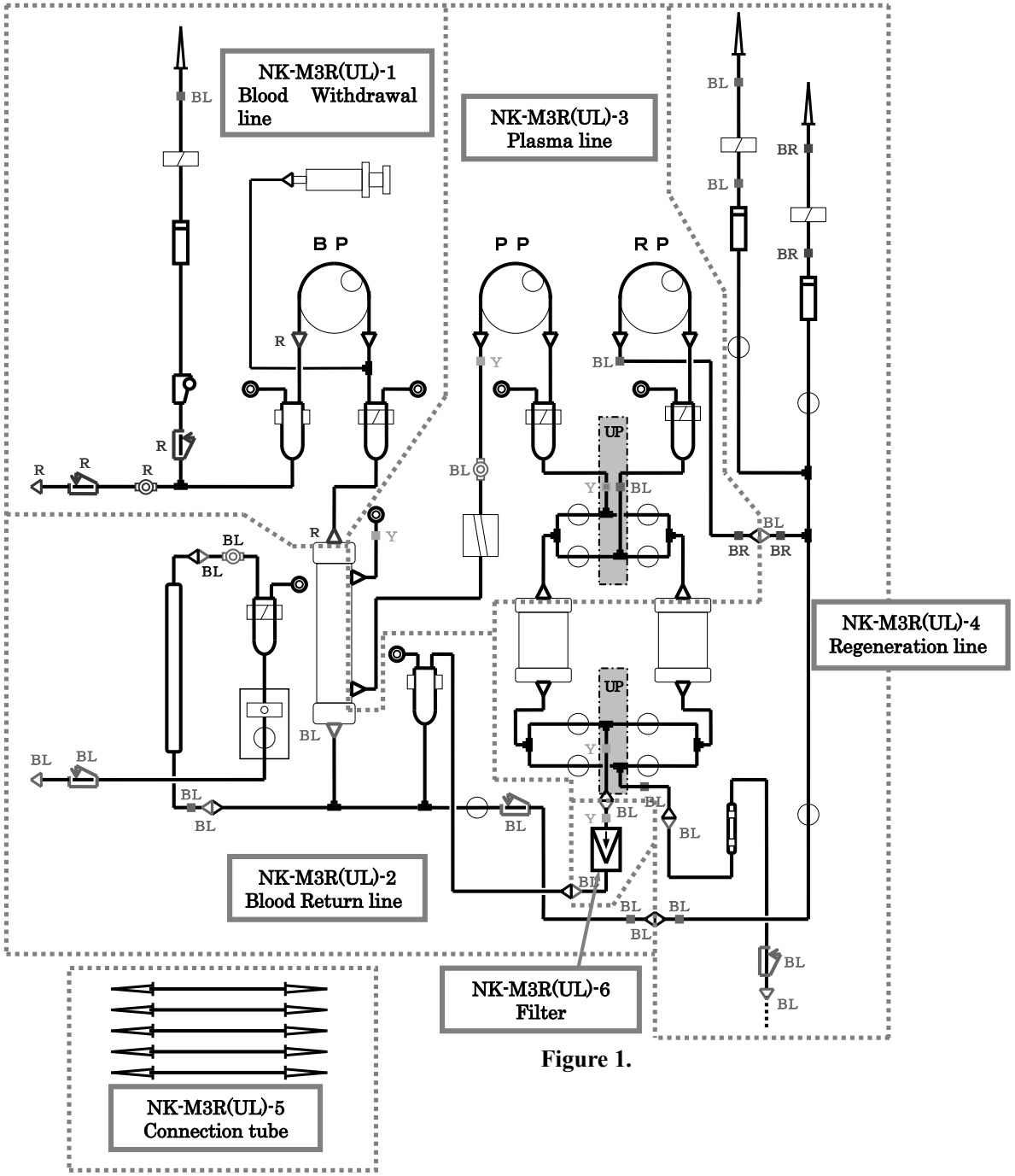
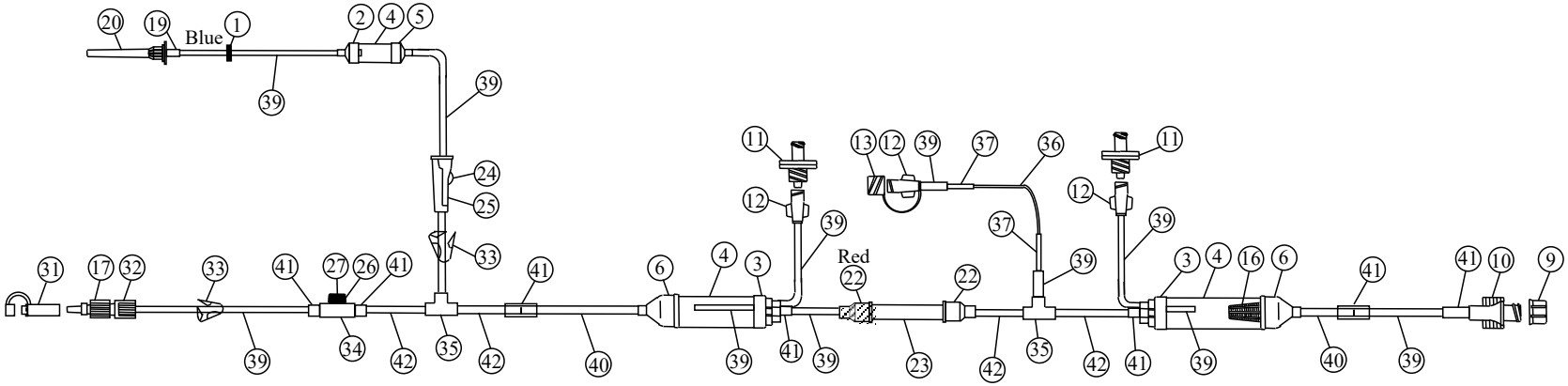


Figure 1.

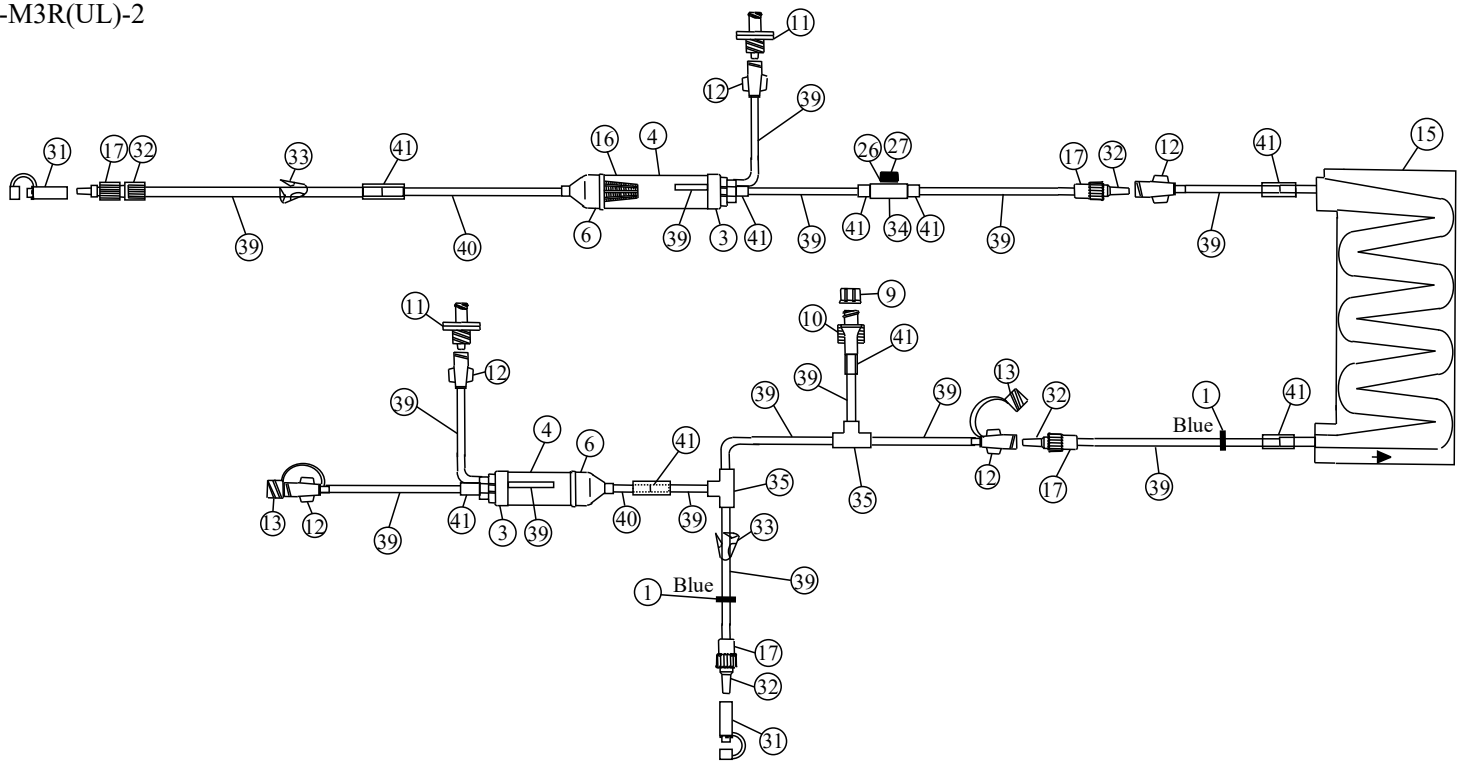
1. BLOOD WITHDRAWAL LINE

Figure 2. NK-M3R(UL)-1



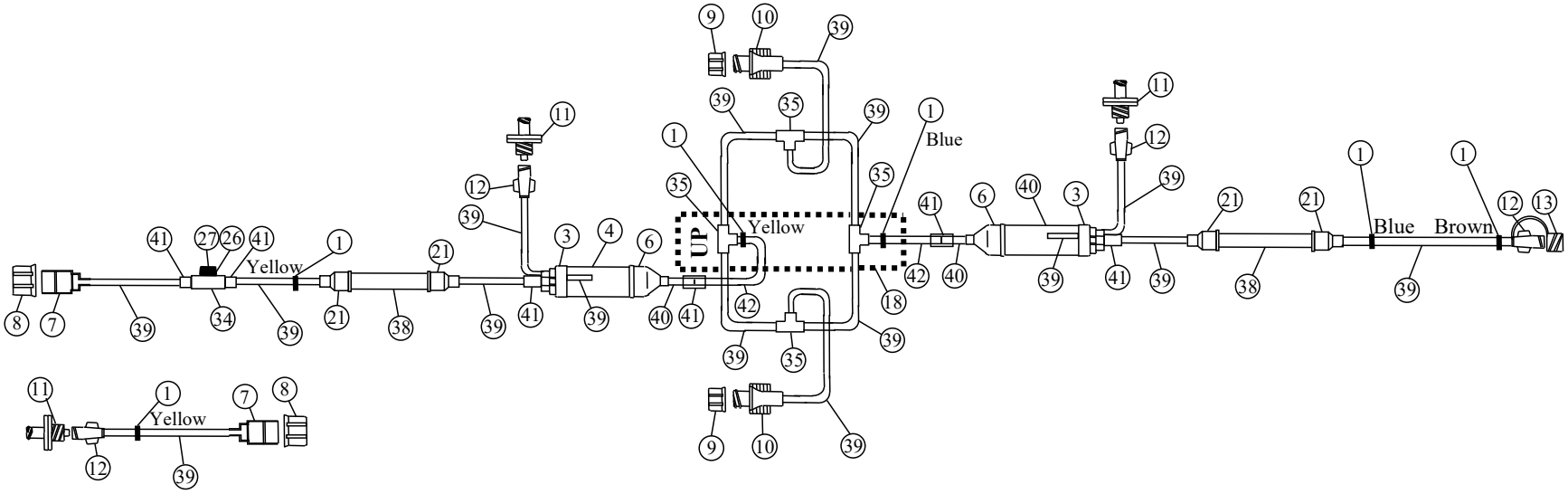
2. BLOOD RETURN LINE

Figure 3. NK-M3R(UL)-2



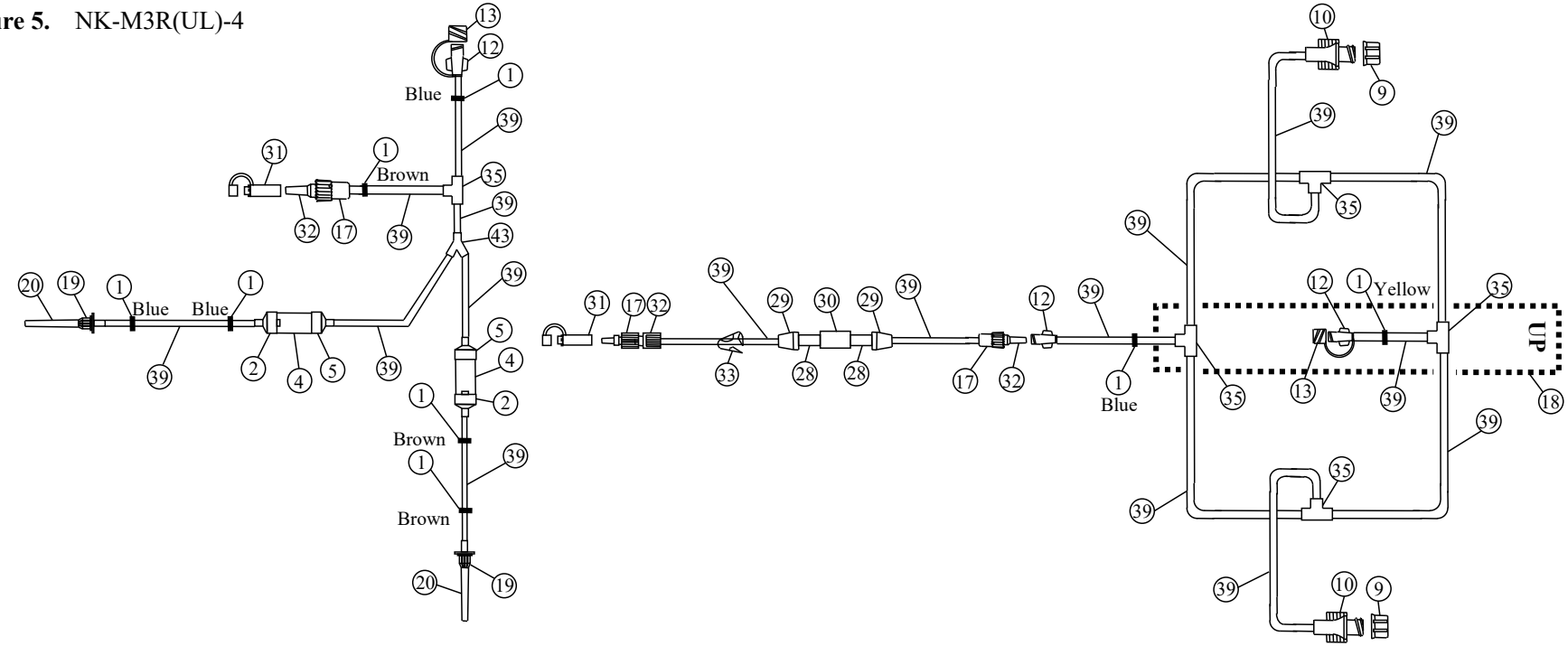
3. PLASMA LINE

Figure 4. NK-M3R(UL)-3



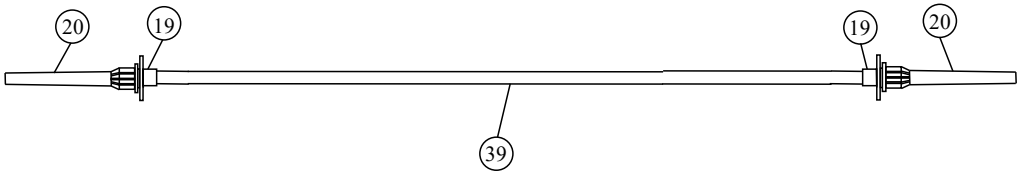
4. REGENERATION LINE

Figure 5. NK-M3R(UL)-4



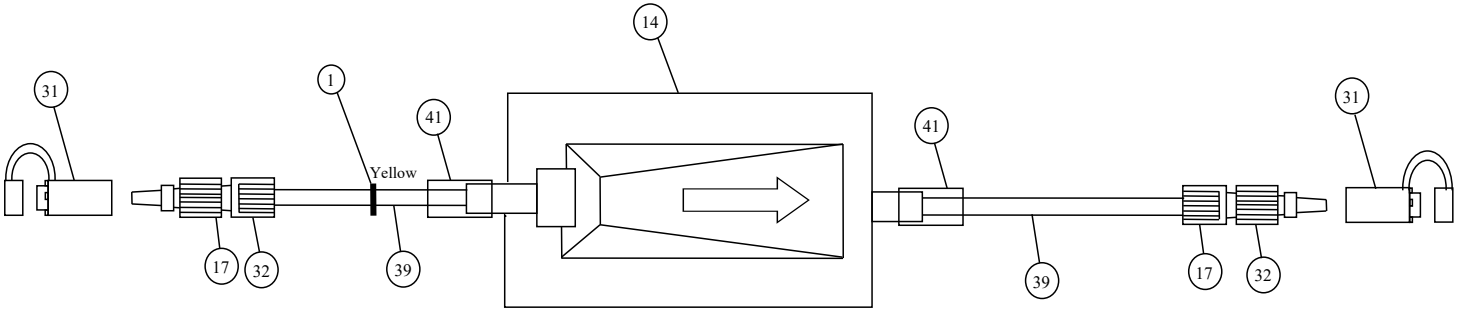
5. CONNECTION TUBE (5)

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	PES / 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

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

Note:
PC Polycarbonate
PVC Polyvinylchloride
PP Polypropylene
PES Polyethersulfone
PTFE Polytetrafluoroethylene

V. Contraindications

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

1. patients who are being treated with angiotensin-converting enzyme (ACE) inhibitors;

   Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER® LA-15 LDL Adsorption Column under concomitant ACE inhibitor medication. Temporal ceasing of ACE inhibitor intake to remove its bioactivity from the patient's blood may not always be sufficient to avoid such adverse reactions. The ACE inhibitors should be switched to another antihypertensive medication (for example, angiotensin II receptor blockers (ARBs)) at the medical discretion of the treating physician.

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 Medical America LLC and use only the disposable device component recommended by Kaneka Medical 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 Medical America LLC or the use of disposable device components not recommended by Kaneka Medical 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) <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 Notes for Potential Adverse Reactions</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>**).

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 ⅔ to ¾ 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 ºC), 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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