



TORAYMYXIN PMX-05R

EXTRACORPOREAL HEMOPERFUSION CARTRIDGE

INSTRUCTIONS FOR USE

Instructions for Use of TORAYMYXIN PMX-05R

Extracorporeal Hemoperfusion Cartridge

•Sterile •Single Use only •Do not re-use •Sterilized by steam •Do not use if the packaging is damaged or open
•Do not use if the sterilization indicator is whitish yellow

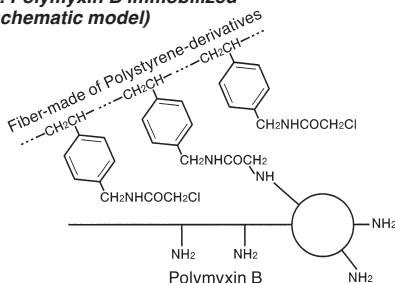
Read Instructions For Use carefully before use.

I. DEVICE DESCRIPTION

TORAYMYXIN PMX-05R (PMX) is an extracorporeal hemoperfusion cartridge intended for the selective removal of endotoxin from circulating blood through direct hemoperfusion (DHP).

The PMX cartridge (cartridge) contains fibers made of polystyrenederivatives (alphachloro-aceto-amidomethylated polystyrene). Polymyxin B is immobilized on the surface of these fibers (see **Figure 1**). This fixed Polymyxin B adsorbs and removes endotoxin from the patient's circulating blood.

Figure 1: Polymyxin B immobilized fibers (schematic model)



Each cartridge contains $15 \pm 2g$ fibers (dry weight) and has a blood volume capacity of 40 ± 3 mL. The dimensions and structure of the cartridge are as follows:

- Length: 133 mm
- Diameter (max): 55 mm
- Housing diameter: 40 mm
- Connection between the cartridge and blood tubing: Luer-lock type connectors

The following additional equipment is needed to carry out treatment with PMX:

- A blood pump for extracorporeal circulation at a blood flow rate of 5 – 200 mL/min, monitors for inlet (Pi) and outlet (Po) pressures and an infusion pump for the administration of anticoagulants,
- Hemoperfusion blood tubing suitable for use with the hemoperfusion pump,
- For extracorporeal circulation by veno-venous access, insert a double lumen catheter into the femoral vein or the subclavian vein. Use appropriate size of catheter and blood access site, depending on the body weight and the condition of the patient.

II. INDICATIONS FOR USE

PMX is indicated for use in the treatment of patients with sepsis or septic shock caused by gram-negative bacteria, who usually meet the following conditions:

- Endotoxemia or suspected gram-negative infection, and
- Systemic Inflammatory Response Syndrome (SIRS),

as defined by the presence of at least two of the following four conditions:

- Fever or hypothermia (body temperature of above 38°C or below 36°C)
- Tachycardia (heart rate of above 90 bpm)
- Tachypnea [(respiratory rate of above 20 breaths/min, or PaCO_2 below 4.3 kPa (32mmHg)]
- White blood cell count of above 12,000 cells/ mm^3 , below 4,000 cells/ mm^3 or above 10% immature (band) forms.

III. CONTRAINDICATIONS

Treatment with PMX is contraindicated in the following patients:

- Patients in whom the use of heparin would cause a tendency to uncontrolled bleeding or for whom adequate anticoagulant therapy cannot be safely achieved, such as patients with hemophilia, or
- Patients with known hypersensitivity to heparin, Polymyxin B or chemicals associated with DHP.

IV. ADVERSE REACTIONS

1. Potential Adverse Events

The adverse events below may occur at any time during PMX treatment.

Table 1 lists the adverse events.

Patients with septic shock usually have severe underlying diseases, including, but not limited to cancer, trauma, and cardiovascular disease. These underlying diseases, deterioration in the patient's state of health and/or death due to the progression of sepsis may be reported as adverse events during or after PMX-DHP.

Table 1. Adverse Events

| Type of Adverse Events |
|---|
| Thrombocytopenia, Decreased blood pressure, Allergy (Erythema, etc.), Shock (Decreased blood pressure, Dyspnea, Tachycardia, Hypothermia, Chest pain, Vomiting, Cyanosis, etc), Anaphylactic shock, Ventricular tachycardia, Ventricular fibrillation, Hypoxemia, Cardio palmus, Air embolism, Infection of entry site, Bleeding at puncture site, Abnormal bleeding (due to heparin), Tachycardia, Increased pressure at the entrance of the blood purifier [This is attributable to the dosage and administration of anticoagulants and pathological conditions in patients], Blood clotting in PMX [Blood clotting is attributable to the dosage and administration of anticoagulants and pathological conditions in patients.] |

2. Adverse Reactions of Polymyxin B

Drug to drug interactions and adverse drug reactions of Polymyxin B

The following drug to drug interactions and adverse drug reactions after oral or local administration of Polymyxin B, immobilized in PMX, are mentioned in the precaution of Instruction for Use of each drugs.

(1) Drug to drug interactions

When Polymyxin B is administered concomitantly with anesthetics, muscle relaxants or aminoglycoside antibiotics, respiratory depression due to a curare-like stabilization effect (neuromuscular blocking action) may occur as a result of drug to drug interactions. Medical personnel must pay sufficient attention to their concomitant use.

(2) Adverse drug reactions

Serious adverse drug reactions: Shock, Deafness, Respiratory depression due to neuromuscular blocking action.

Other adverse drug reactions: Renal disorder, Paresthesia, Dizziness, Headache, Pyrexia, Lethargy, Ataxia, Visual disturbance, Rash, Pruritus, Nausea, Vomiting, Anorexia, Diarrhea, Formication, Numbness of tongue, Numbness of lips.

V. WARNINGS AND PRECAUTIONS



1. Warnings

- (1) The PMX cartridge is a disposable medical device intended for single use only. Do not reuse the cartridge. Reuse of the PMX cartridge might cause following adverse events and malfunctions, such as, infection caused by microbiological contamination, adverse reactions caused by residual reprocessing agents and/or residual blood components and performance changes caused by deterioration of device components.
- (2) The PMX cartridge is designed for use in DHP. Do not use in a plasmapheresis procedure.
- (3) Ensure that the blood flows in the direction as indicated by the arrow on the label of the cartridge.
- (4) The PMX cartridge is designed for treatment using unfractionated heparin as an anticoagulant. The safety and efficacy of PMX treatment using other anticoagulants including, but not limited to, low molecular weight heparin (LMWH) or citrate preparations, have not been established. The anticoagulant is required to prevent thrombus formation within the extracorporeal circuit. Anticoagulation with too much heparin is associated with an increased risk of bleeding, especially after a surgical operation.
- (5) It is essential to rinse and then prime the blood tubing and the cartridge with appropriate solutions (see Rinsing and Priming Procedure) in order to rinse out the acidic solution in the cartridge and to restore the physiological conditions.
- (6) The inlet pressure of the cartridge should be below 33 kPa (250 mmHg). The maximum tolerable pressure of the cartridge is 66 kPa (500 mmHg). If an unusual pressure difference (approx. 26.4 kPa (200 mmHg)) is observed between the inlet and outlet of the cartridge, clotting in the cartridge must be suspected.
- (7) If the tubing is equipped with an air bubble detector, connect the outlet tubing to it. This will minimize the

risk of air embolism.

2. Precautions

1) General Precautions

- (1) PMX should only be administered by personnel who have been properly trained in extracorporeal therapies.
- (2) At all times during PMX treatment, medical personnel must monitor the patient for the symptoms of adverse events, in particular for decreased blood pressure, thrombocytopenia and allergy. It is recommended to monitor blood pressure during PMX-DHP and to measure platelet counts before and after PMX-DHP.
- (3) If treatment with three cartridges per cycle is not effective, other treatment should be applied.
- (4) PMX should be used in patients with endotoxemia or suspected gram-negative infection, after the outcome of treatment, including antibiotic therapy, is confirmed sufficiently.
- (5) PMX must be carefully used in patients treated with anesthetics, muscle relaxants or aminoglycoside antibiotics, since respiratory depression due to a curare-like stabilization effect (neuromuscular blocking action) may occur as a result of drug to drug interactions.
- (6) Medical personnel must pay sufficient attention to a decrease in the patient's body temperature. The extracorporeal circuit and patient should be adequately warmed if necessary.
- (7) Medical personnel must pay special attention to the treatment of patients whose renal function is impaired. A small possibility exists that a very small amount of Polymyxin B (less than 1 ppb) remaining in the cartridge even after rinsing with saline could be infused into the patient. The risks associated with the intravenous injection of Polymyxin B include nephrotoxic and neurotoxic side effects which are exacerbated by impaired renal function, high serum levels of Polymyxin B and/or concurrent use of other nephrotoxic/neurotoxic drugs. Signs of nephrotoxicity caused by Polymyxin B include, but are not limited to, albuminuria, azotemia, rising BUN or urea and diminishing urine output. Signs of neurotoxicity include, but are not limited to, irritability, progressive weakness, drowsiness, ataxia, paresthesia, numbness, blurred vision and possible neuromuscular blockade.
- (8) PMX must be used carefully in the elderly, while monitoring their condition, because of their general decline in physiologic function.
- (9) Since the safety of PMX treatment during pregnancy has not been established, the treatment must be applied for pregnant and potentially pregnant women only in the case therapeutic benefits are considered to exceed the risks.
- (10) PMX has been used for pediatrics and neonates. However, since the treatment experiences are fewer than that for adults, the safety of the treatment has not been established. Refer to related guidelines and publications (if available) when applying the treatment to pediatrics and neonates.
- (11) The safety of PMX-DHP performed directly in conjunction with the use of any other blood purification cartridge including continuous renal replacement therapy (CRRT) has not been established. It is recommended to carry out PMX-DHP prior to any

other blood purification therapy if needed. If other blood purification therapy has already been initiated prior to the PMX-DHP, it is recommended to interrupt the blood purification therapy in order to carry out the PMX-DHP.

- (12) Check all connections of the extracorporeal circuit carefully prior to and during the procedure. At all times avoid kinking of the tubing lines and the vascular catheter.
- (13) If the extracorporeal circuit is equipped with a drip chamber, ensure that the drip chamber is at all times at least 2/3 to 3/4 full and monitored at all times in order to decrease the risk of air embolism.
- (14) Ensure that the fluid circuit for PMX-DHP, including the blood tubing and double lumen catheter for blood access is sterile and non-pyrogenic. Use aseptic handling techniques to maintain these conditions. Before use, check the packaging of all the disposables to ensure that it is intact. Do not open the pouch containing the disposables until immediately prior to use.
- (15) Follow the normal practice of the healthcare facility with regard to screening for Hepatitis B and other infectious diseases. Universal precautions should be taken at all times to prevent exposure to and transmission of infectious agents.

2) Precautions relating to heparin administration

- (1) The recommended heparin doses for PMX-DHP are as follows ⁽¹⁾:

- Priming 4 Units (U)/mL ⁽²⁾
- Bolus 40 — 60 U/kg
- Maintenance 20 U/kg body weight/hr ⁽³⁾

⁽¹⁾ These doses are general recommendation for adult patients. Adjust the dose depending on the body weight and the condition of the patient, especially when applying to low body weight patients.

⁽²⁾ The heparin solution (2,000 U/ 500 mL physiological saline) is used for priming.

⁽³⁾ The maximum maintenance dose allowed for any patient is 2,000 U/hr.

- (2) The heparin doses described above and the ACT (activated clotting time) value described below (see (4)) are intended as general recommendations. 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.
- (3) The heparin dose can be adjusted during and after PMX-DHP on the basis of clinical observation; ACT and/or APTT (activated partial thromboplastin time) values. (Some patients, in particular patients who have undergone surgery, may not be able to tolerate the above recommended levels of heparin. This may be due to: (a) presence of a continuous heparin infusion or regular administration of heparin prior to treatment with PMX-DHP and/or (b) high ACT or APTT value prior to treatment with PMX-DHP.)
- (4) Closely monitor patient clotting time at intervals during the procedure to ensure that an adequate level of anticoagulant is maintained. Adjust the continuous infusion of heparin based on the ACT or APTT measurement. Maintain ACT or APTT within the range

150 — 180 sec or 50 — 60 sec with a maximum of 240 sec or 100 sec, respectively. Blood for ACT or APTT measurement must be taken from the first sampling port on the inlet line (before the heparin line joins the inlet line).

3) Precautions for storage and handling

- (1) The cartridge housing is made of plastic. Avoid any physical shock while transporting and handling, as damage to the housing or other components may result. Do not tap the cartridge with any metallic objects.
- (2) Store cartridge in a dry area at normal room temperature, away from direct sunlight. Do not freeze.
- (3) Use the cartridge before the "Use by" date given on the product label, preceded by the symbol.



4) Precautions before initiating PMX treatment

- (1) Do not use the cartridge if any of the following conditions are observed, since sterility of the cartridge may have been compromised:
 - Any damage to the cartridge;
 - Any damage to the single-unit packaging (pouch) containing the cartridge, or if the pouch is opened;
 - The presence of droplets on the inner surface of the pouch;
 - Loose or absent end-caps on the inlet and/or outlet.
- (2) The cartridge has been sterilized by steam. Check the sterilization indicator on the single-unit packaging of the cartridge. The indicator changes to dark brown when the cartridge has been sterilized. If the indicator is whitish yellow the cartridge has not been sterilized. Do not use the cartridge if the sterilization indicator is whitish yellow.
- (3) Use aseptic handling technique, including the use of protective gloves and glasses, while connecting the blood infusion line to the cartridge and returning the blood from the cartridge.
- (4) The saline solution in the cartridge is acidic (about pH 2.0) due to steam sterilization. Use 2 L or more of physiological saline solution to rinse out the acidic solution in the cartridge and restore the physiological conditions so that they are compatible with human body fluid.
- (5) At all times ensure there is no fluid leakage between the blood tubing and the cartridge connector.
- (6) Do not allow air bubbles to enter the cartridge during the rinsing and priming procedure. Use the cartridge promptly after rinsing and priming.
- (7) Check also the following items before initiating PMX treatment:
 - Proper connection between the catheter and the blood tubing
 - Proper connection between the blood tubing and the inlet and outlet of the cartridge
 - Alarms and detectors of the hemoperfusion machine are operational.

5) Precautions during PMX treatment

- (1) Ensure that the blood flow rate is maintained at a minimum of 20 mL/min during extracorporeal circulation, to avoid risk of stasis in the cartridge.
- (2) The inlet pressure must not exceed 66 kPa (500 mmHg). Inlet pressure higher than 66 kPa (500 mmHg) may cause leak in the cartridge or disconnection between the blood tubing and the cartridge connector.

- (3) Monitor the inlet and outlet pressures in the system during PMX-DHP.
- (4) If an unusual pressure difference (approx. 26.4 kPa (200 mmHg)) is observed between the inlet and outlet of the cartridge, clotting in the cartridge must be suspected. If the inlet pressure is increasing, appropriate measures should be taken such as change the flow rate, additional administration of anticoagulant and/or saline flush.
- (5) Ensure there is no blood leakage between the blood tubing and cartridge connector.

6) Precautions at the end of PMX treatment

- (1) Use sufficient normal physiological saline (approximately 500 mL) to ensure adequate blood return.
- (2) When recovering the blood, reverse the position of the cartridge, so that the arrow is pointing down, and allow the blood to flow in the direction of the arrow. This will reduce the amount of blood remaining within the cartridge.
- (3) For low body weight patients, return the blood with slow flow rate in order to avoid excess circulating blood volume. When priming volume is more than 10% of circulating blood volume, return the blood in the cartridge and tubing to blood bag if necessary.
- (4) When disposing of the cartridge and blood tubing, ensure compliance with all local requirements and the policy of the healthcare facility regarding precautions for and prevention of infection and environmental pollution.

VI. USE OF THE PMX CARTRIDGE

The procedures described below are indicated as general procedures. The prescribing/attending physician should select the appropriate procedures based on the specific tubing and machine used in the PMX treatment.

1. Rinsing and Priming Procedure

Observe proper aseptic technique, including the use of protective gloves and glasses, while handling the cartridge and blood connections.

The following quantities of infusion solution will be needed:

- Physiological saline: at least 2 L
- Heparinized saline: at least 500 mL
- Physiological saline (for blood return): approximately 500 mL

Refer to the instructions for use for the chosen blood tubing.

1) Rinsing the blood tubing

- (1) Rinse and fill the arterial line with physiological saline and ensure that there are no air bubbles present.
- (2) See **Figure 2**. Put the drip chamber of the Venous line on a stand using a cartridge holder or clamp. Connect the pressure monitoring line to the outlet pressure (Po) monitor. Ensure that the connector of the fluid level adjusting line is closed, using a clamp if necessary. Clamp the Venous line near the catheter connector.
- (3) Place the cartridge in the normal position (arrow pointing up). Remove the cap on the outlet connector and attach the Venous line to it. Turn the cartridge upside down (arrow pointing down). Remove the cap from the cartridge inlet. Gently press the drip chamber of the Venous line to drive out any air in the cartridge inlet (see **Figure 3**). If any air bubbles

remain, inject a small amount of physiological saline, using a syringe. As soon as physiological saline is seen in the tip of the cartridge inlet, connect the Arterial line to the cartridge. During this process, take care to prevent air entering the connector. Return the cartridge to its normal position (arrow pointing up).

- (4) Remove the clamp near the catheter connector on the Venous line. Operate the blood pump to pass 2 L or more of physiological saline at the flow rate of 100 mL/min. Be sure to flow the solution from bottom to top (from the arterial to the venous end) for adequate rinsing. At the start of rinsing, tap the cartridge gently with the hand and drive out the air bubbles, until no more bubbles come out of the cartridge. Do not tap the cartridge with any metallic objects.
- (5) After rinsing, stop the blood pump, and re-clamp near the catheter connector on the Venous line. Prepare to prime the lines and cartridge with heparinized saline as follows.

2) Priming the cartridge and blood lines

Ensure that priming is performed with heparinized saline.

- (1) Put 2,000 U of heparin into 500 mL of physiological saline (4 U/mL).
- (2) Connect a 500 mL bag of the heparinized saline to the infusion line.
- (3) Remove the clamp on the Venous line near the catheter connector. Operate the blood pump. Allow 500 mL of heparinized saline to flow, at a flow rate of 100 mL/min to replace the solution inside the cartridge and the tubing with heparinized saline.
- (4) During this process, also prime the inside of the heparin line and the lines on the inlet line.
- (5) For low body weight patients, especially when priming volume is more than 10% of circulating blood volume, use appropriate priming methods including the use of blood products, depending on the body weight and the condition of the patient.

2. Operating Procedure (See **Figure 4**)

The basic conditions of the operating procedure are as follows:

- Method: direct hemoperfusion (DHP)
- Blood flow rate: 20 – 40 mL/min
- Duration of DHP: 2 hours
- Anticoagulant ^(*): heparin 40 – 60 U/kg as bolus and 20 U/kg body weight/hr as continuous infusion

^(*) These doses are general recommendation for adult patients. Adjust the dose depending on the body weight and the condition of the patient, especially when applying PMX to low body weight patients.

- (1) Connect the Arterial line to the patient's catheter on the outlet lumen of the catheter.
- (2) Operate the blood pump, initially at a low flow rate. Monitor the patient's condition, and when necessary, drive out small amount of priming solution, depending on the body weight and the condition of the patient.
- (3) Connect the Venous line to the patient's catheter on the inlet lumen of the catheter (see **Figure 5**).
- (4) Ensure the cartridge is upright (arrow pointing up). Flow the blood from the arterial end up to the venous end following the direction of the arrow shown on the label and carry out DHP.

- (5) Administer the heparin bolus and then proceed with the continuous infusion. For heparin doses, refer to "Precautions relating to heparin administration" above.
- (6) Gradually increase the blood flow rate, and ensure that a blood flow rate of 30 (20 – 40) mL/min is maintained during extracorporeal circulation.
- (7) The duration of extracorporeal circulation is 2 hours per cartridge.

3. Finishing Procedure

1) Normal Condition

- (1) Prepare 500 mL of physiological saline as replacement fluid for blood recovery.
- (2) Once extracorporeal circulation has been completed, stop the blood pump. Lock the catheter on the Arterial line, clamp and remove the Arterial line from the patient. Reverse the position of the cartridge so that the arrow points down. Operate the blood pump, and while monitoring the patient's condition, flow physiological saline at a low flow rate to return the blood in the cartridge and tubing to the patient. Adjust the volume and flow rate depending on the body weight and the conditions of the patient. Depending on the conditions, blood return may not be necessary.
- (3) Lock the catheter at the Venous line, clamp and remove the Venous line from the patient.

2) Abnormal Condition (clotting within the cartridge)

- (1) If the inlet pressure is increasing, appropriate measures should be taken such as change the flow rate, additional administration of anticoagulant and/or saline flash.
- (2) Remove the Arterial line from the catheter. Operate

the blood pump at a low flow rate and return blood from the blood tubing and cartridge to the patient. Adjust the volume and flow rate depending on the body weight and the conditions of the patient. Depending on the conditions, blood return may not be necessary.

4. Disposing of the Cartridge

When disposing of the cartridge components and other tubing waste, ensure compliance with all local requirements and the policy of the healthcare facility regarding precautions for and prevention of infection and environmental pollution.

VII. REFERENCES

- (1) Hisataka Shoji, Kazuyoshi Hanasawa, Masashi Kodama Extracorporeal endotoxin removal by Polymyxin-B immobilized fiber cartridge; designing and antiendotoxin efficacy in clinical application. *Therapeutic Apheresis* 1998; 2:3 – 12.
- (2) Masashi Kodama, Tohru Tani, Kazuyoshi Hanasawa, et al. Treatment of sepsis by plasma endotoxin removal; hemoperfusion using a polymyxin-B immobilized column. *J. Endotoxin Res.* 1997; 4: 293 – 300.
- (3) Tohru Tani, Kazuyoshi Hanasawa, Yoshihiro Endo, et al. Therapeutic apheresis for septic patients with organ dysfunction: Hemoperfusion using a polymyxin-B immobilized column. *Artificial Organs* 1998; 22: 1038 – 1044.

VIII. WARRANTY LIMITATIONS

The manufacturer, Toray Industries Inc., warrants that the TORAYMYXIN PMX-05R cartridge (cartridge) has been manufactured in accordance with their specifications and in compliance with good manufacturing practices,

Figure 2

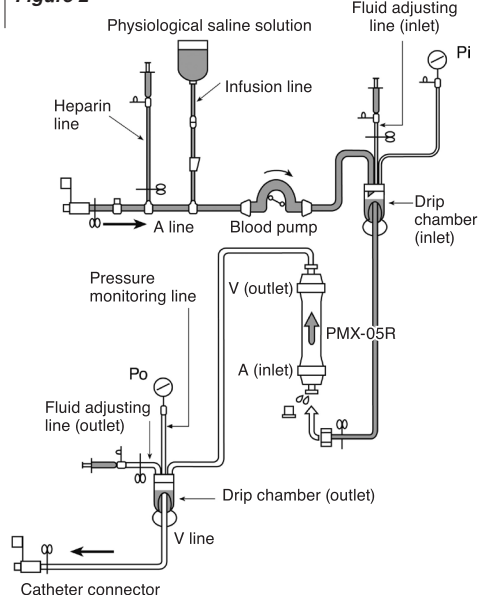


Figure 3

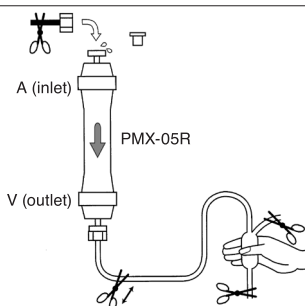
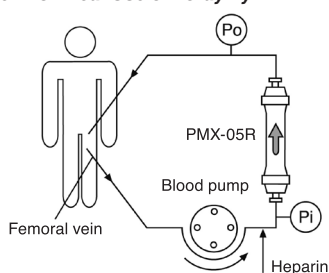


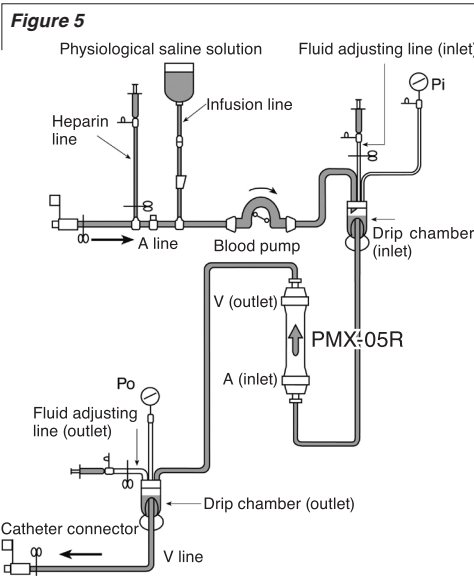
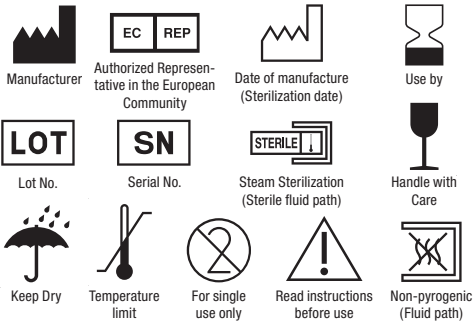
Figure 4: Clinical Use of Toraymyxin



other applicable industry standards and regulatory requirements. Toray Industries Inc.'s quality system is operated in accordance with International and European standards for quality systems, as assessed by the Notified Body TÜV SÜD Product Service.

The manufacturer shall not be liable for any misuse, improper handling, operation or storage, non-compliance with the warnings and instructions for use, damage arising from events after the manufacturer's release of the cartridge including use after the labeled expiration date. In addition, Toray Industries Inc. is not responsible for any damage caused by reprocessing or reuse of the cartridge.

IX.Explanation of symbols used on the device labelling:



'TORAY'



Manufacturer:

Toray Industries, Inc.

1-1, Nihonbashi-Muromachi 2-chome, Chuo-ku, Tokyo 103-8666, JAPAN

Exporter:

Toray Medical Co., Ltd.

4-1, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo 103-0023, JAPAN



Toray International Italy S.r.l.

Via Mecenate 86, 20138 Milan, ITALY