

*FDA has authorized the emergency use of CytoSorb 300 mL device:

CytoSorb 300mL device is manufactured under and ISO 13485 and CE Mark approved

INTRODUCTION

1.1. Intended Use

The CytoSorb Device (CytoSorb) is a non-pyrogenic, sterile, single-use device containing adsorbent polymer beads designed to remove cytokines, as blood passes through the device. CytoSorb is placed in a blood pump circuit.

1.2. Indications

CytoSorb is indicated for use in conditions where elevated levels of cytokines are present.

Maximum Treatment Time per Device: 24 hours.

Administration of Therapy:

Day 1: Change device every 12 hours;

Day 2: Change device at 24 hours;

Day 3: Change device at 24 hours.

Clinical assessment to be made after 72 hours of use to determine if patient is receiving clinical benefit for for continuation of therapy. (**see Section 11: Addendum to IFU for further guidance**).

Maximum Blood Flow Rate: 700 mL/min

Minimum Blood Flow Rate: 100 mL/min

Recommended Blood Flow Rate: 150-500 mL/min

Flow rates below 150 mL/min may be required due to limitations of the catheter access, caution should be used at low flow rates as the potential for clotting may increase.

1.3. Contraindications

- Patients with very low platelet counts (< 20,000/ μ L).
- Any pre-existing contraindication to extracorporeal therapy
- Known allergies to extracorporeal circuit components
- History of heparin-induced thrombocytopenia
- Acute sickle cell crisis.
- Morbid obesity with BMI \geq 40 kg/m²
- Any pre-existing advanced medical disease with life-expectancy less than 1 month
- Treatment deemed clinically futile
- Pregnancy

1.4. Relative Contraindications

- Concomitant use of corticosteroids
- Patients who are profoundly immune suppressed

1.5. General Precautions and Warnings

- **CAUTION:** FDA has authorized the emergency use of CytoSorb 300 mL device in COVID-19 Patients
- CytoSorb should only be administered by personnel who have been properly trained in administration of extracorporeal therapies. Complications associated with extracorporeal therapies include: blood loss due to leaks, hypothermia, dyspnea, hypoxia/hypotension, and death due to air embolism.
- The extracorporeal circuit should be monitored continuously during treatment for blood leaks. In the event of a blood leak during treatment the healthcare provider should respond according to the facility's established protocols.
- Discretion should be used when treating a patient weighing less than 100 lb. (45 kg).
- CytoSorb will affect trans membrane pressure (TMP) if CytoSorb is placed distal to the dialyzer membrane. In such cases, use only CRRT equipment where an integral weight scale is available that will self-correct for ultrafiltration volume for changes in TMP. To minimize chances of clotting in this setting, pre-dilution is recommended.
- Many patients with COVID-19 infection are known to be hyper-coagulable. Refer to Section 3.1 for specific guidance regarding anticoagulation.

1.6. Warnings Related to Drug Removal

Hydrophobic drugs may be removed by the device.

Data on removal of antiviral medication is unfortunately still scarce. Results from animal studies point to very low removal of Ganciclovir, and anecdotal reports on CytoSorb therapy in influenza patients receiving Oseltamivir did not state any evidence of removal. There is no available data on the removal of remdesivir. Removal of hydroxychloroquine and azithromycin by CytoSorb is possible. Due to the large size of tocilizumab (148 kDa), convalescent plasma antibodies (>150 kDa), and other biologics of similar size, these are NOT expected to be removed by CytoSorb.

The physician is advised to measure concomitant drug concentrations, where a test exists, after CytoSorb treatment and adjust drug dosing accordingly (**see Section 11: Addendum to IFU for further guidance**).

In addition, when nutritional supplementation is indicated, the physician is encouraged to administer gastric or other internal tube feeding rather than total parenteral intravenous nutrition and lipids. Lipid or fat emulsions may negatively affect CytoSorb. If lipids (e.g. lipid containing parenteral nutrition) are clinically indicated, then the physician is advised to administer these after CytoSorb treatment is completed or discontinue administration two (2) hours prior to the next CytoSorb treatment.

1.7. WARNING: Air entering the extracorporeal circuit during treatment can result in clotting of the device, serious injury, or death. Check the integrity of all bloodlines and connections prior to the initiation of blood perfusion and periodically during the treatment. The venous return line or drip chamber should be continuously monitored with an air detector.

1.8. Side Effects

In rare cases, hypersensitivity reactions may occur during extracorporeal treatment. A history of allergies (polystyrene/divinylbenzene, polycarbonate, polypropylene, silicone and polyester) is an indication requiring careful monitoring for hypersensitivity reactions. In the event of a hypersensitivity reaction, treatment must be discontinued and aggressive, first line therapy for anaphylactoid reaction must be initiated. The decision to return the blood to the patient encountering a hypersensitivity reaction must be made by a physician.

Reduction in serum albumin and related reduction in total calcium were noted in a clinical study of CytoSorb use in cardiopulmonary bypass procedures. Clinicians should monitor albumin and calcium levels during treatment.

The patient should also be monitored for other clinical events associated with extracorporeal treatment, including but not limited to:

Hemodynamic compromise (e.g., hypotension, increased vasopressor requirement, reduced cardiac perfusion)	Risks related to vascular access placement (e.g., infection, blood loss, thrombosis, tissue/organ injury)
Arrhythmia	Risks related to anticoagulation (e.g., blood loss, allergic reaction)
Blood loss	change in body temperature
Thrombosis	muscle cramping
Air embolism	Headache
Infection	Nausea
Hemolysis	Vomiting
Thrombocytopenia / leukopenia	Fever
Unintended removal of other blood substances (e.g., vitamins, proteins, medications)	Pruritus

1.9. CytoSorb is a single-use device and cannot be reused. CytoSorb must be stored/used within the temperature range of 1 – 40°C.

2. PREPARATION FOR TREATMENT

2.1. CytoSorb is intended for use with standard, commercially available bloodlines compatible with the pump system used (see Section 10: Ancillary Equipment List). Female blood line DIN connectors are required to connect with CytoSorb blood ports. CytoSorb may be used with extracorporeal blood pumps, e.g. intermittent hemodialysis, continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO) equipment where hemofilters/dialyzers are used.

CAUTION: Pressure monitoring of the bloodline between the blood pump and CytoSorb is recommended. If the pump system is not equipped with a pressure sensing device for this line, use of an accessory pressure monitoring device is recommended.

CAUTION: In the case of ECMO, CytoSorb placement should be in a shunt off of the main flow as is the current practice with hemoconcentrators, and flow monitoring (≤ 700 mL/min.) is recommended, e.g. ultrasonic flow probe. A

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flow rate of 600 mL/min through CytoSorb circuit will shunt approximately 20% of the blood flow from the patient. Total ECMO flow rate should be adjusted to ensure delivery of desired flow to patient.

2.2. The fluid pathway in an intact device inside the protective pouch is sterile. Inspect the protective pouch for any sign of damage to CytoSorb. Carefully remove CytoSorb from the pouch and examine for defects.

CAUTION: DO NOT USE CytoSorb if it appears to be damaged. DO NOT USE CytoSorb if beads appear to be free-floating within the endcaps.

2.3. When renal replacement therapy (dialysis, hemofiltration) is required, CytoSorb may be placed upstream (proximal) or downstream (distal, with equipment with integral weight scale) of the hemofiltration/dialysis device.

2.4. Locate the blood inlet (arterial) end of the device. With the inlet end of CytoSorb facing downward, firmly secure the device in a vertical position to the pump system's device holding pole (or alternate device holding system) using a standard hemofilter/dialyzer clamp. Leave the port plugs in place.

CAUTION: Assure all Blood Lines Are Primed With Saline Before Connecting CytoSorb!

WARNING: Do not allow air to enter device as this may cause clotting and reduced efficacy of the device.

Priming by Gravity: Aseptically connect to a 0.9% sterile isotonic saline bag with a clamped standard priming line (spike or luer to female DIN-lock line) and standardized adapters if required. Prime lines completely. Connect the saline primed blood supply line (and adapter if required) of pump circuit to CytoSorb blood inlet port. Now remove CytoSorb outlet port plug and connect venous priming line (and adapter if required) with CytoSorb outlet port and a waste bag. Open clamps on lines, flush CytoSorb and priming lines using a minimum of 2 liters sterile isotonic saline in total for both priming of the lines and CytoSorb flush. Disconnect and discard the waste bag when complete. Clamp inlet and outlet lines.

Note: Gently thump the outlet side of CytoSorb with the palm of your hand during priming to remove air.

Priming by Pump (e.g. standalone configuration): Prime the blood supply line of pump circuit and adapter, if required, using 0.9% sterile isotonic saline. Remove CytoSorb inlet port plug and connect the saline primed blood supply line to the CytoSorb inlet port. Now remove CytoSorb outlet port plug and connect venous priming line (and adapter if required) with CytoSorb outlet port and a waste bag. Open clamps on lines, turn on pump and prime (flush) device at a flow of ~150 mL/min., using a minimum of 2 liters sterile isotonic saline total for both priming of the lines and CytoSorb flush. Disconnect and discard the waste bag when complete and connect blood return line of pump circuit to CytoSorb outlet port and clamp inlet and outlet lines.

Note: Gently thump the outlet side of CytoSorb with the palm of your hand during priming to remove air.

CAUTION: Avoid the entry of air into CytoSorb. Rinse always to waste bag.

3. INITIATION OF TREATMENT

3.1. Anticoagulation

Clinical experience suggests COVID-19 patients require higher anticoagulation at start of treatment to prevent circuit clot off. The following heparin anticoagulation guidelines are based on clinical experience and can be combined with platelet inhibition by acetylsalicylic acid (**see Section 11: Addendum to IFU for further guidance**).

Heparin: For COVID-19 Patients the following are provided as guidelines:

- **70 IU per kg body weight (BW) loading dose**
- **15- 20 IU per kg BW/ hour maintenance dose**

PTT should be monitored closely, e.g. every 4 hours at the start of therapy. Patient shall be anticoagulated to an ACT of 160 – 210 seconds or an aPTT of 60 – 80 seconds or higher, with a preference for the high end of the range for patients who are hypercoagulable (e.g., elevated levels of D-dimer, etc.), prior to the start of treatment for CRRT or hemoperfusion. Clinicians shall monitor and maintain these levels throughout the treatment. Patients undergoing ECMO should be anticoagulated according to standard clinical practice for those procedures.

Note: Anticoagulation should only be by heparin. The device may remove other anticoagulants and antiplatelet

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agents, and these cannot be used. This includes Factor Xa inhibitors, direct thrombin inhibitors, GP2B3A inhibitors, P2Y₁₂ inhibitors, etc.

3.2. Confirm configuration of device set-up as shown in figures provided in Section 9.

3.3. Initiate treatment as prescribed by a physician and directed by this document while referring to the blood pump Instructions for Use regarding pump set-up and operation.

4. During Treatment

4.1. Monitor the pressure in the extracorporeal circuit, including the line between the blood pump and CytoSorb, if available. Investigate any indication of abnormal pressure.

4.2. Visually inspect CytoSorb for any signs of clotting or blood leaks from the circuit or within the dialyzer. Report all clotting or blood leaks to the responsible medical professional.

4.3. Periodically monitor the extracorporeal circuit for evidence of obstruction, security of fittings, and air within the circuit.

5. Termination of Treatment

5.1. When the treatment is completed, terminate the treatment as directed by the Instructions For Use included with bloodlines and blood pump circuit. As is standard practice, upon completion of CytoSorb therapy, it is recommended that blood in the device and lines be returned to the patient.

5.2. Discard the bloodlines and CytoSorb in an appropriate biohazard waste receptacle.

CAUTION: CytoSorb is a single-use only device and is not for reuse. Attempts to reuse CytoSorb may result in secondary infection, device clotting and/or a biohazardous situation.

6. Performance Characteristics

Flow Resistance (HCT 32 ± 3% @ 37 ± 1° C)	
Qb ≤ 700 mL/min:	140 mmHg
Qb ≤ 500 mL/min:	90 mmHg
Qb ≤ 200 mL/min:	30 mmHg
Blood Priming Volume:	150 mL
Maximum Blood Flow Rate:	700 mL/min
Minimum Blood Flow Rate:	100 mL/min
Recommended Blood Flow Rate:	150-500 mL/min
Maximum Pressure Limit:	760 mmHg
Storage Fluid:	Isotonic Saline
Priming Fluid:	Isotonic Saline

7. Blood Contact Materials

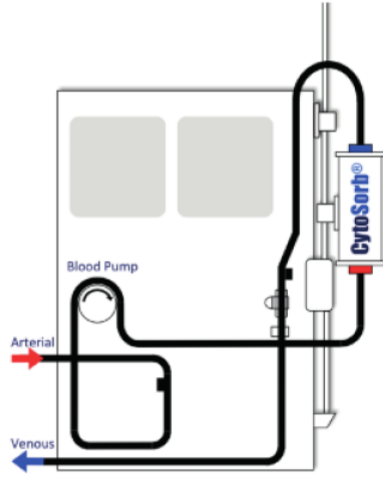
Adsorbent Material:	Crosslinked Divinylbenzene/polyvinylpyrrolidone
Housing:	Polycarbonate
O-ring Seals:	Silicone
Screen:	Polyester/Polypropylene

8. Training Technical Support

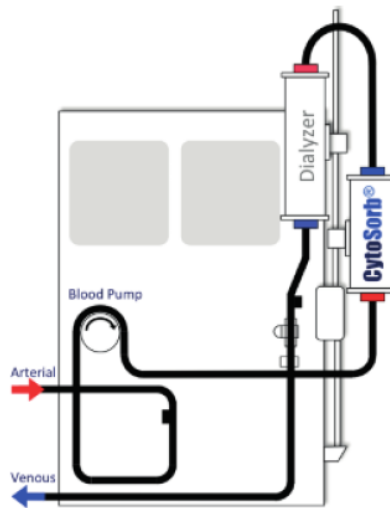
Training and Technical Support can be requested by calling 732-482-1511

9. CytoSorb Use Configurations

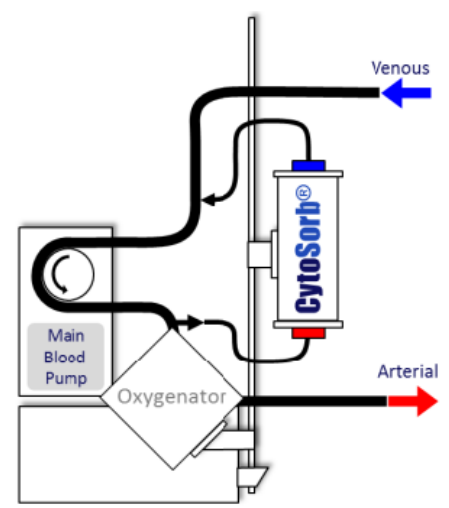
CytoSorb is intended to be used in a veno-venous configuration only, with the exception of VA-ECMO.



Hemoperfusion



CytoSorb + CRRT



ECMO



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www.cytosorbents.com

10. Ancillary Equipment List for Use with CytoSorb[®]

1. Tubing Kit – CRRT & ECMO

The parts below are sourced from suppliers outside of CytoSorbents and utilized with a CytoSorb[®] device to allow for adaptation to a hospital's available extracorporeal circuit (i.e. CRRT, ECMO, hemoperfusion, etc):



Part #	QTY	Product Name/Description	Source/Manufacturer
AMS-184-1	2	Bag Spike Line male luer	Health Care Technology Inc.
MPC-865	2	Female to Male Din Connector	Molded Products, Inc
MPC-850-16	1	Din to Din 16" Connector	Molded Products, Inc
MPC-660S	1	Din to Din 36" Connector with Sample Port	Molded Products, Inc
66425/4	1	2-L Metrix Bag	Health Care Technology Inc.
MPC-160	2	F-F Connector (Optional)	Molded Products, Inc

All products listed above are standard parts and 510(k) cleared for sale and distribution in the US.

General Instructions for Installation and Use





The following are general instructions for installation of the CytoSorb device into an extracorporeal Circuit utilizing the above equipment list. Clinicians will receive training on how to properly install and operate the CytoSorb device by CytoSorbents personnel and a train the trainer model will be implemented. CytoSorbents will continue to offer and provide additional training as requested and provide "on-call" customer support to support clinical application of the CytoSorb Device

1. Connect AMS-184-1 to MPC-865 and then connect this to MPC-850-16.
2. Spike the prime fluid with AMS-184-1 and allow fluid to fill the entire tubing ensuring that there is no air present in the line.
3. Clamp the primed line.
4. Connect the open end of AMS-184-1 to the inferior (Inlet) side of the CytoSorb device.
5. Connect MPC-660S to the superior (outlet) side of the CytoSorb device.
6. Connect the open side of MPC-660S to the remaining MPC-865.
7. Connect the open end of MPC-865 to the remaining AMS-184-1.
8. Utilize the spike of AMS-184-1 to secure the line to the 66425/4.
9. Ensure that all connections are secure and the CytoSorb is perpendicular to the floor.
10. Prime the CytoSorb device with 2L of your priming fluid.
11. Clamp all lines once priming is complete and assess the available connections for the extracorporeal circuit.
12. Optional Step – MPC-160 (2) may be utilized on either end of your lines if a female to female connector is required
13. Remove both AMS-184-1 lines and secure connection of the CytoSorb device to the extracorporeal circuit.
14. Initiate flow through the CytoSorb device.
15. The CytoSorb and associated tubing should be monitored periodically to ensure no leakage occurs.

Part #	Image
AMS-184-1	
MPC-865	

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MPC-850-16		
MPC-660S		
66425/4		
MPC-160		

2. Pole Clamp



11. Addendum to IFU: Additional Guidance For Device Use In COVID-19 Patients

1. Frequency of changing of device:

- a) First 24 hours of device use – change device every 12 hours.
- b) After 24 hours of device use – change device every 24 hours.

2. Administration of Therapy

The initial duration of CytoSorb therapy is **72 hours** to determine if the patient is receiving clinical benefit on pulmonary status and/or hemodynamic status as assessed by the Treating Physician. If the patient is receiving benefit within the first 72 hours, CytoSorb therapy may be continued until the patient is deemed clinically stable enough to discontinue CytoSorb therapy (e.g., reversal of shock, weaning from ventilation), at the discretion of the Treating Physician. If the patient is not receiving clinical benefit within 72 hours, CytoSorb therapy is to be discontinued. CytoSorb therapy can be discontinued at any time if it is deemed in the welfare of the patient.

3. Special considerations for anticoagulation for extracorporeal circuits:

- a) Heparin – Clinical experience suggests COVID-19 patients require higher anticoagulation at start of treatment to prevent circuit clot-off. The following heparin anticoagulation guidelines are based on clinical experience; this can be combined with platelet inhibition by acetylsalicylic acid.

Heparin: For COVID-19 Patients the following are provided as guidelines:

- 70 IU per kg body weight (BW) loading dose
- 15- 20 IU per kg BW/ hour maintenance dose

PTT should be monitored closely, e.g. every 4 hours at the start of therapy. Patient shall be anticoagulated to an ACT of 160 – 210 seconds or an aPTT of 60 – 80 seconds or higher, with a preference for the high end of the range for patients who are hypercoagulable (e.g., elevated levels of D-dimer, etc.), prior to the start of treatment for CRRT or hemoperfusion. Clinicians shall monitor and maintain these levels throughout the treatment. Patients undergoing ECMO should be anticoagulated according to standard clinical practice for those procedures.

Note: Anticoagulation should only be by heparin. The device may remove other anticoagulants and antiplatelet agents, and these cannot be used. This includes Factor Xa inhibitors, direct thrombin inhibitors, GP2B3A inhibitors, P2Y₁₂ inhibitors, etc.

3. Removal of drugs by the device:

Hydrophobic drugs may be removed by the device. Data on removal of antiviral medication is unfortunately still scarce. Results from animal studies point to very low removal of Ganciclovir, and anecdotal reports on CytoSorb therapy in influenza patients receiving Oseltamivir did not state any evidence of removal. There is no available data on the removal of remdesivir. Removal of hydroxychloroquine and azithromycin by CytoSorb is possible. Due to the large size of tocilizumab (148 kDa), convalescent plasma antibodies (>150 kDa), and other biologics of similar size, these are NOT expected to be removed by CytoSorb. The following modifications to drug dosing are recommended:

- a) Choosing a dosage for antiviral (or antibiotic) therapy at the upper end of the recommended range or 1.5-2.0x the normal dose, depending on the drug and therapeutic window.
- b) Perform therapeutic drug monitoring wherever possible.
- c) Do not administer the drugs in-line with the CytoSorb device where immediate removal is possible.
- d) Allow time for tissue distribution and cellular uptake following antibiotic administration, where blood purification is less likely to impact the effect of the antibiotic. This may be accomplished by administering the antibiotic during device changes, or before or after treatment. If not possible, then an alternative is to administer an additional dose of the antibiotic 1-2 hours after the start of each new CytoSorb cartridge

CytoSorb[®]
300 mL Device

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Treatment of COVID-19**

Concomitant use of corticosteroids is not recommended as they may delay viral clearance, increase risk of secondary bacterial and fungal infections, and may be removed by the CytoSorb device.

12. CytoSorbents Complaint Handling Procedure

Please complete those items highlighted in **gray** and return to CytoSorbents by one of the following Methods:

1. Email: complaints@cytosorbents.com
2. FAX US +01-732-329-8650

ATTENTION



Reportable Events Timeline: 24 Hour Reportable and Other Complaints

24 Hour Reportable Event

Patient Death or Serious Injury or Malfunction.

A Serious Injury is any event that:

- Is life-threatening,
- Results in permanent impairment of a body function or permanent damage to a body structure, or
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

A malfunction means:

- The failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled.

Immediately, but not later than 24 hours after awareness of the event, contact should be via email to complaints@cytosorbents.com **and** fax to CytoSorbents **01-732-329-8650**

Other Complaints:

Complaints are any deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the device.

All other complaints must be reported as soon as possible (max. 10 Days) to CytoSorbents!!!
Patient injury or death thought to be associated with the device must be dealt with promptly.
Please collect the information regarding circumstances surrounding the death and device association with the incident.

Complaint Handling Form

Additional information may be attached as required.

Complaint Reference Number: CRN xxx - xxx

(Assigned by CytoSorbents Inc.)

Complaint Received From:

(Name, Title (if applicable), Company, Address, Phone Number, Email Address – Include as Much Information as Possible – 250 Character Maximum)

Event Awareness Date:

Date the Event was Reported:

Complaint Reported By: Physician Nurse Distributor Perfusionist Other:

Mode of Communication of Complaint: Phone Facsimile Email Other:

Type of Complaint: Clinical Functional Other:

Complaint Received By: *(60 Characters Maximum)*

Complaint Form Initiation Date:

Device Name (and Reference Number, if applicable):

Lot(s) and Serial Number(s) (if applicable):

Defective Quantity:

Quantity Delivered:

Received By:

Quantity Returned:

Date of Receipt:

Complaint: *(310 Character Maximum)*

Pump System Used:

Indication:

Comments: *(250 Character Maximum)*

Action(s) Taken: *(250 Character Maximum)*

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