April 22, 2020

Mr. Tito Aldape (Fortunato)
Director, Global Regulatory Affairs, Acute Therapies
Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, IL 60015

Dear Mr. Aldape:

This letter is in response to Baxter Healthcare Corporation's request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of the oXiris Set device[1] to treat patients 18 years of age or older with confirmed Coronavirus Disease 2019 (COVID-19) admitted to the intensive care unit (ICU) with confirmed or imminent respiratory failure in need of blood purification, including use in continuous renal replacement therapy, to reduce pro-inflammatory cytokines levels, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19.[2] Pursuant to section 564 of the Act, and on the basis of such determination, the Secretary of HHS then declared on March 24, 2020, that circumstances exist justifying the authorization of emergency use of medical devices, including alternative products used as medical devices, due to shortages during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.[3]

There are no FDA approved, licensed, or cleared device treatments for COVID-19. Based on bench performance testing and reported clinical experience, FDA has concluded that the oXiris Set device may be effective at treating certain patients with confirmed COVID-19 by removing various pro-inflammatory cytokines from their blood. FDA believes, based on the totality of scientific evidence available, that the removal of pro-inflammatory cytokines may ameliorate

[1] The oXiris Set was first CE-marked in December 2007 and marketed in the EU in December 2008. Multiple other Regions/Countries have registered oXiris for patients in need of blood purification, including continuous renal replacement therapy, and in conditions where excessive endotoxin and inflammatory mediator levels exist.
[2] U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. 85 FR 7316 (February 7, 2020).
[3] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 17335 (March 27, 2020).

cytokine storm due to the overabundance of pro-inflammatory cytokines and, in turn, provide clinical benefit.

Having concluded that the criteria for issuance of this authorization under section 564(c) of the Act are met, I am authorizing the emergency use of the oXiris Set device as described in the Scope of Authorization (Section II) of this letter, subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the oXiris Set device as described in the Scope of Authorization (Section II) of this letter to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure in need of blood purification, including use in continuous renal replacement therapy, meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

1. SARS-CoV-2, the virus that causes COVID-19, can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the oXiris Set device may be effective in treating patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure in need of blood purification, including use in continuous renal replacement therapy, and that the known and potential benefits of the oXiris Set device, when used to treat such patients, outweigh the known and potential risks of the oXiris Set device; and

3. There is no adequate, approved, and available alternative to the emergency use of the oXiris Set device for the treatment of these COVID-19 patients.[4]

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the oXiris Set device to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure in need of blood purification, including use in continuous renal replacement therapy, by reducing pro-inflammatory cytokine levels, which may ameliorate a cytokine storm due to the overabundance of pro-inflammatory cytokines and, in turn, provide clinical benefit to such patients. For the purposes of this EUA, a patient with confirmed COVID-19 who is admitted to the ICU with confirmed or imminent respiratory failure in need of blood purification, including use in continuous renal replacement therapy, is a patient 18 years of age or older who has any one of the following conditions:

[4] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

a) Early acute lung injury (ALI)/early acute respiratory distress syndrome (ARDS); or

b) Severe disease, defined as:

1) dyspnea,
2) respiratory frequency ≥ 30/min,
3) blood oxygen saturation ≤ 93%,
4) partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
5) lung infiltrates > 50% within 24 to 48 hours; or

c) Life-threatening disease, defined as:

1) respiratory failure,
2) septic shock, and/or
3) multiple organ dysfunction or failure.

Authorized Product Details

1. The oXiris Set device is comprised of the following components and materials:

The oXiris Set (oXiris) is a disposable, extracorporeal circuit for use only with the Prismaflex or PrisMax control unit.

The oXiris Set consists of:

- a heparin grafted hollow fiber hemofilter/dialyzer
- a tubing circuit
- a cartridge plate
- an effluent bag 5LT

The hemofilter/dialyzer is made of specialized hollow fiber membrane with an effective surface area of 1.5 m^2.

This hollow fiber membrane is composed of:

- a copolymer of acrylonitrile and sodium methylal sulfonate (AN69)
- a surface treatment agent: Polyethyleneimine (PEI)
- heparin that is grafted on the membrane

The fluid pathways of the oXiris Set are sterile and non-pyrogenic. The oXiris Set is sterilized by ethylene oxide.

2. The oXiris Set device mechanism of function is as follows:

Blood enters the filter via a blood inlet port where it is distributed to the hollow fibers. The patient's blood flows inside the hollow fibers and exits the device via a blood exit port.

By means of hydrostatic pressure or transmembrane pressure which is created by a combination of positive and negative pressures across the membrane, plasma water along with certain lower and middle molecular weight solutes pass through the membrane and into the dialysate/filtrate compartment of the device. Considering the AN69 membrane microstructure and chemical composition, toxins having basic residues on the surface can also be adsorbed by means of ionic interactions in the bulk and/or at the blood/membrane interface. Due to the specific coating of the fiber, endotoxins can also be adsorbed by means of ionic interactions at the membrane surface.

When this device is used with the Baxter PrismaFlex or PrisMax control unit, toxins and waste products are removed from the patient's blood by means of diffusion, convection, and adsorption; they are eliminated via the dialysate/filtrate and the membrane during the treatment session. The dialysate/filtrate exits the devices via a dialysate outlet port.

The oXiris Set is a disposable, extracorporeal circuit for use with the PrismaFlex control unit or with the PrisMax control unit. The oXiris Set consists of a hollow fiber hemofilter/dialyzer with an internal surface permanently grafted with highly purified heparin from porcine origin, and tubing lines. The oXiris Set enables removal of various inflammatory mediator by diffusion, convection, and adsorption.

Due to the dense negatively charged functional groups, oXiris removes positively charged inflammatory mediators by adsorption. The positively charged PEI middle layer, which is achieved by surface treatment of the base material (AN69) adsorbs endotoxins, and also enables heparin grafting. The adsorption of endotoxins occurs directly between the excess positive charges of the PEI and the negative charges of the lipopolysaccharides (LPS) moieties.

3. The following device settings have been validated for operation of the oXiris Set device:

	oXiris
PHYSICAL CHARACTERISTICS [1]	
Membrane effective surface area	1.5 m^2
Fiber internal diameter (wet) Fiber wall thickness	240 µm 50 µm
Blood volume in set	193 mL
Overall dimensions • Length • Width • Height	 27 cm 22 cm 9 cm
Weight	890 g
Heparin grafted	4500 ± 1500 IU/m^2
OPERATING PARAMETERS	
Maximum TMP	450 mmHg 60 kPa
Maximum blood pressure	500 mmHg 66.6 kPa
Minimum blood flow rate Maximum blood flow rate	100 mL/min 450 mL/min

Additional treatment information has been provided in the oXiris Set Instructions for Use, which is authorized under this EUA.

The oXiris Set device, when labeled consistently with the labeling authorized by FDA, entitled "oXiris Set Instructions for Use" (available at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations), which may be revised in consultation with, and with concurrence of, the Division of Renal, Gastrointestinal, Obesity and Transplant Devices (DHT3A)/Office of GastroRenal, ObGyn, General Hospital and Urology Devices (OHT3)/Office of Product Evaluation and Quality (OPEQ)/Center for Devices and Radiological Health (CDRH), is authorized under the terms and conditions of this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

The oXiris Set device is authorized to be accompanied by the following product-specific information pertaining to the emergency use, which is required to be made available to healthcare providers and patients:

- Fact Sheet for Healthcare Providers: Emergency Use of the oXiris Set Device for COVID-19
- Fact Sheet for Patients: Emergency Use of the oXiris Set device for COVID-19

I have concluded, pursuant to section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of the oXiris Set device, when used to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure in need of blood purification, including use in continuous renal replacement therapy, when used consistently with the Scope of Authorization of this letter (Section II), outweigh the known and potential risks of this product.

I have concluded, pursuant to section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the oXiris Set device may be effective in treating patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure in need of blood purification, including use in continuous renal replacement therapy, when used consistently with the Scope of Authorization of this letter (Section II), pursuant to section 564(c)(2)(A) of the Act.

FDA has reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, and concludes that the oXiris Set device, when used to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure in need of blood purification, including use in continuous renal replacement therapy, (as described in the Scope of Authorization of this letter (Section II)) meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the authorized product under this EUA must be consistent with, and may not exceed, the terms of this letter, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section IV). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the oXiris Set device, with the required labeling set forth in this section (Section II), is authorized to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure in need of blood purification, including use in continuous renal replacement therapy, by reducing cytokine levels (associated inflammatory response).

III. Waiver of Certain FDA Requirements

Pursuant to Section 564(e)(3) of the Act, with respect to the emergency use of a product for which an authorization under this section is issued, FDA may waive or limit, to the extent appropriate given the circumstances of the emergency, requirements regarding good manufacturing practice otherwise applicable to the manufacture, processing, packing, or holding of products subject to regulations under this Act, including such requirements established under sections 520(f)(1). FDA grants that waiver, including waiver from the quality system requirements under 21 CFR Part 820.

IV. Conditions of Authorization

Pursuant to section 564(e) of the Act, I am establishing the following conditions on this authorization:

Baxter Healthcare Corporation

A. Baxter Healthcare Corporation must comply with the labeling requirements under 21 CFR 801 Subpart A (general labeling provisions) and 21 CFR 801.109 (labeling for prescription devices), as well as those described in Section II, Scope of Authorization. As such, compliance with the unique device identification regulations (see Subpart B of 21 CFR Part 801) is not required under this EUA.

B. Baxter Healthcare Corporation may request changes to the authorized labeling and fact sheets. Such requests will be made in consultation with, and require concurrence of, DHT3A/OHT3/OPEQ/CDRH.

C. Baxter Healthcare Corporation may request changes to the components and materials. Such requests will be made in consultation with, and require concurrence of, DHT3A/OHT3/OPEQ/CDRH.

D. Baxter Healthcare Corporation may request changes to the Scope of Authorization (Section II in this letter) of your product. Such requests will be made in consultation with DHT3A/OHT3/OPEQ/CDRH, and require concurrence of, Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC) and DHT3A/OHT3/OPEQ/CDRH.

E. Baxter Healthcare Corporation may request the addition of other instruments and associated software for use with your product. Such requests will be made in consultation with, and require concurrence of, DHT3A/OHT3/OPEQ/CDRH.

F. Baxter Healthcare Corporation will have a process in place to collect information on the performance of their products and for reporting adverse events. . Adverse events of which the Baxter Healthcare Corporation becomes aware will be reported to FDA under 21 CFR Part 803.

G. Baxter Healthcare Corporation is authorized to make available additional information relating to the emergency use of the product that is consistent with, and does not exceed, the terms of this letter of authorization.

H. Baxter Healthcare Corporation will notify FDA of any authorized distributor(s) of the product, including the name, address, and phone number of any authorized distributor(s), and provide authorized distributor(s) with a copy of this EUA.

Baxter Healthcare Corporation and Authorized Distributor(s)[5]

I. Baxter Healthcare Corporation and authorized distributor(s) will make oXiris Set devices available with the authorized labeling and fact sheets, described in the Scope of Authorization (Section II) of this letter.

[5] "Authorized Distributor(s)" are identified by the sponsor in EUA requests as an entity allowed to distribute the product.

J. Baxter Healthcare Corporation and authorized distributor(s) will make available on their website(s) the Fact Sheet for Healthcare Providers and the Fact Sheet for Patients.

K. All descriptive printed matter relating to the use of the oXiris Set shall be consistent with the authorized labeling and fact sheets. No descriptive printed matter relating to the use of the oXiris Set may represent or suggest that this product is safe or effective for the prevention or treatment of COVID-19.

L. Baxter Healthcare Corporation and authorized distributor(s) will ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

M. Through a process of inventory control, Baxter Healthcare Corporation and authorized distributor(s) will maintain records of the healthcare settings to which they distribute the oXiris Set and number of oXiris Set they distribute.

N. Baxter Healthcare Corporation and authorized distributor(s) are authorized to make available additional information relating to the emergency use of the product that is consistent with, and does not exceed, the terms of this letter of authorization.

Conditions Related to Advertising and Promotion

O. All advertising and promotional descriptive printed matter relating to the use of the oXiris Set device shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

P. No advertising or promotional descriptive printed matter relating to the use of the oXiris Set device may represent or suggest that such products are safe or effective for the prevention or treatment of COVID-19.

Q. All advertising and promotional descriptive printed matter relating to the use of the oXiris Set device clearly and conspicuously shall state that:

- the oXiris Set device has neither been cleared or approved for the indication to treat patients with COVID-19 infection;
- the oXiris Set device has been authorized by FDA under an EUA;
- the oXiris Set device is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of medical devices under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

V. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of medical devices is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

Sincerely,

Denise M. Hinton -S3

Digitally signed by Denise M. Hinton -S3
Date: 2020.04.22 20:10:03 -04'00'

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures