May 8, 2020

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, IL 60047

Attention: Molly Ventrelli
Senior Vice President, Regulatory Affairs

Dear Ms. Ventrelli:

This letter is in response to your May 1, 2020, request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of Fresenius Propoven 2% Emulsion to maintain sedation via continuous infusion in patients greater than 16 years old who require mechanical ventilation in an Intensive Care Unit (ICU) setting during the 2019 coronavirus disease (COVID-19) pandemic, as described in the Scope of Authorization (Section II) of this letter, 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 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.[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to Section 564 of the Act, subject to terms of any authorization issued under that section.[2]

Fresenius Propoven 2% Emulsion is an intravenous (IV) sedative hypnotic drug that can be utilized to maintain sedation via continuous infusion in patients greater than 16 years old with suspected or confirmed COVID-19 who require mechanical ventilation in an ICU setting.

Based on published data from China and preliminary reports in the U.S., it has been noted that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, has led to an increased population with critical illness, necessitating sedation drug products for mechanically ventilated patients. As a result, there is a shortage of FDA-approved propofol available for use in mechanically ventilated critically ill patients, as well as shortages of

[1] 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. February 4, 2020.*
[2] 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 18250 (April 1, 2020).

alternative FDA-approved drugs, dexmedetomidine and midazolam, which are approved for sedation of mechanically ventilated patients in the ICU setting. Based on the totality of scientific evidence available, FDA has concluded that it is reasonable to believe that the Fresenius Propoven 2% Emulsion may be effective to maintain sedation via continuous infusion in patients greater than 16 years old with suspected or confirmed COVID-19 who require mechanical ventilation in an ICU setting.

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 your Fresenius Propoven 2% Emulsion, 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 Fresenius Propoven 2% Emulsion, as described in the Scope of Authorization (Section II) of this letter, to maintain sedation via continuous infusion in patients greater than 16 years old who require mechanical ventilation in an ICU setting, meets the criteria for issuance of an authorization under Section 564(c) of the Act, because I have concluded that:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness requiring mechanical ventilation, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that Fresenius Propoven 2% Emulsion may be effective to maintain sedation via continuous infusion in patients greater than 16 years old with suspected or confirmed COVID-19[3] who require mechanical ventilation in an ICU setting, and that, when used under the conditions described in this authorization, the known and potential benefits of Fresenius Propoven 2% Emulsion when used for the indication above outweigh the known and potential risks of such products; and

3. There is no adequate, approved, and available alternative to the emergency use of Fresenius Propoven 2% Emulsion due to shortages of FDA-approved alternatives during the COVID-19 pandemic.[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 as follows:

- Fresenius Propoven 2% Emulsion will be used only to maintain sedation via continuous infusion in patients greater than 16 years old who require mechanical ventilation.

[3] In the circumstances of this public health emergency, it would not be feasible to require healthcare providers to seek to limit Fresenius Propoven 2% Emulsion only to be used for patients with suspected or confirmed COVID-19; therefore, this authorization does not limit use to such patients.
[4] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

- Fresenius Propoven 2% Emulsion will be administered only by a licensed healthcare provider in an ICU setting.
- Fresenius Propoven 2% Emulsion will not be administered to pregnant women, unless there are no FDA-approved products available to maintain sedation for these patients should they require mechanical ventilation in an ICU setting.
- Fresenius Propoven 2% Emulsion will be used only in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

Product Description

Fresenius Propoven 2% Emulsion (propofol) is classified as a sedative hypnotic drug. It is an injectable emulsion containing 20 mg/mL of propofol for continuous IV administration to maintain sedation in patients greater than 16 years old who require mechanical ventilation in an ICU setting.

Fresenius Propoven 2% Emulsion is authorized to be accompanied by the following product-specific information pertaining to emergency use (referred to as "authorized labeling"), which is required to be made available to healthcare providers and patients respectively:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Fresenius Propoven 2% Emulsion
- Fact Sheet for Patients and Parent/Caregivers: Emergency Use Authorization (EUA) of Fresenius Propoven 2% Emulsion
- Diprivan and Fresenius Propoven 2% Emulsion Comparison Wall Chart
- Fresenius Propoven 2% Emulsion Advisory Stickers on double strength concentration for application to vial cap ("Advisory Stickers")

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 Fresenius Propoven 2% Emulsion, when used to maintain sedation via continuous infusion in patients greater than 16 years old with suspected or confirmed COVID-19 who require mechanical ventilation in an ICU setting when used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

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 Fresenius Propoven 2% Emulsion may be effective to maintain sedation via continuous infusion in patients greater than 16 years old with suspected or confirmed COVID-19 who require mechanical ventilation in an ICU setting when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that Fresenius Propoven 2% Emulsion (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the

Conditions of Authorization (Section IV). Subject to the terms of an 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), Fresenius Propoven 2% Emulsion is authorized to maintain sedation via continuous infusion in patients greater than 16 years old with suspected or confirmed COVID-19[5] who require mechanical ventilation in an ICU setting as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Fresenius Kabi USA, LLC

A. Fresenius Kabi USA, LLC may request changes to the authorized labeling as described in the Scope of Authorization (Section II) of this letter. Such requests will be made in consultation with, and require concurrence of, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAMPM)/Office of Neuroscience (ON)/Office of New Drugs (OND)/Center for Drug Evaluation and Research (CDER), as appropriate.

B. Fresenius Kabi USA, LLC may request changes to the Scope of Authorization (Section II in this letter) of the product. Such requests will be made in consultation with, and require concurrence of, the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC) and DAAMPM/ON/OND/CDER.

C. Fresenius Kabi USA, LLC will manufacture Fresenius Propoven 2% Emulsion in conformance with cGMPs and all appropriate specifications.

D. Fresenius Kabi USA, LLC will perform and document process validation for Fresenius Propoven 2% Emulsion in 100 mL vials concurrently with the first manufactured batches. Additionally, Fresenius Kabi USA, LLC will add at least three representative lots of Fresenius Propoven 2% Emulsion to the firm's stability program.

E. Fresenius Kabi USA, LLC will report to FDA serious adverse events and all medication errors associated with the use of the Fresenius Propoven 2% Emulsion of which they become aware during the pandemic, to the extent practicable given emergency circumstances, using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

[5] See footnote 3.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

Submitted reports under both options should state: "use of Fresenius Propoven 2% Emulsion was under an EUA". For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

Fresenius Kabi US, LLC and Authorized Distributors[6]

F. Fresenius Kabi USA, LLC 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.

G. Fresenius Kabi USA, LLC and authorized distributor(s) will make Fresenius Propoven 2% Emulsion available with the authorized labeling as described in the Scope of Authorization (Section II) of this letter.

H. Fresenius Kabi USA, LLC and authorized distributor(s) will make available on their website(s) the Fact Sheet for Healthcare Providers and the Fact Sheet for Patients and Parent/Caregivers.

I. Through a process of inventory control, Fresenius Kabi USA, LLC and authorized distributor(s) will maintain records of the healthcare settings to which they distribute Fresenius Propoven 2% Emulsion and the number of Fresenius Propoven 2% Emulsion they distribute.

J. Fresenius Kabi USA, LLC 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.

K. Fresenius Kabi USA, LLC 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.

Hospitals and Other Healthcare Facilities to Whom the Authorized Fresenius Propoven 2% Emulsion Is Distributed and Healthcare Providers Administering the Authorized Fresenius Propoven 2% Emulsion

L. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized labeling (as described in the Scope of Authorization (Section II) of this letter) is made available to healthcare providers and to patients and caregivers through appropriate means.

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

M. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized Fresenius Propoven 2% Emulsion (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, days of infusion per patient, other drugs administered).

N. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Fresenius Kabi USA, LLC and/or FDA. Such records will be made available to Fresenius USA, LLC, HHS, and FDA for inspection upon request.

O. Healthcare facilities and prescribing health care providers or their designee receiving Fresenius Propoven 2% Emulsion will track all medication errors associated with the use of and all serious adverse events that are considered to be potentially attributable to Fresenius Propoven 2% Emulsion use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers using one of the following methods:

Option 1: Complete and submit a MedWatch form online (www.fda.gov/medwatch/report.htm)

Option 2: Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (this form can be found via link above).

Call 1-800-FDA-1088 for questions. Submitted reports should state, "use of Fresenius Propoven 2% Emulsion was under an EUA" at the beginning of the question "Describe Event" for further analysis.

Conditions Related to Printed Matter, Advertising and Promotion

P. All descriptive printed matter, including advertising and promotional material, relating to the use of the Fresenius Propoven 2% Emulsion 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.

Q. No descriptive printed matter, including advertising or promotional material, relating to the use of the Fresenius Propoven 2% Emulsion may represent or suggest that such products are safe or effective.

R. Except for the Advisory Stickers described in Section II, all descriptive printed matter, including advertising and promotional material, relating to the use of Fresenius Propoven 2% Emulsion clearly and conspicuously shall state that:

- the Fresenius Propoven 2% Emulsion is not FDA-approved;
- the Fresenius Propoven 2% Emulsion has been authorized by FDA for use under an EUA;

- the Fresenius Propoven 2% Emulsion is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biologics for prevention and treatment of COVID-19 is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures