March 12, 2021

B. Braun Melsungen AG
Attention: Rebecca Stolarick
Registered Agent
901 Marcon Boulevard
Allentown, PA 18109

RE: Emergency Use Authorization 096

Dear Ms. Stolarick:

This letter is in response to your request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of Propofol-Lipuro 1% injectable emulsion for infusion 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 biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act, subject to terms of any authorization issued under that section.[2]

Propofol-Lipuro 1% injectable emulsion for infusion 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.

The Agency has 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,

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[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).

necessitating sedation drug products for mechanically ventilated patients. As a result, there is an insufficient supply of the FDA-approved propofol available for use in mechanically ventilated critically ill patients.[3] Based on the totality of scientific evidence available, FDA has concluded that it is reasonable to believe that the Propofol-Lipuro 1% injectable emulsion for infusion 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 Propofol-Lipuro 1% injectable emulsion for infusion, 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 Propofol-Lipuro 1% injectable emulsion for infusion, as described in the Scope of Authorization (Section II) of this letter, 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 Propofol-Lipuro 1% injectable emulsion for infusion may be effective to maintain sedation via continuous infusion in patients greater than 16 years old with suspected or confirmed COVID-19[4] who require mechanical ventilation in an ICU setting, and that, when administered as described in the Scope of Authorization (Section II) and used under the conditions described in this authorization, the known and potential benefits of Propofol-Lipuro 1% injectable emulsion for infusion outweigh the known and potential risks of such product; and
3. There is no adequate, approved, and available alternative to the emergency use of Propofol-Lipuro 1% injectable emulsion for infusion due to insufficient supplies of FDA-approved alternatives to fully meet the emergency need during the COVID-19 pandemic.[5]

[3] FDA also assessed the supply of FDA-approved alternatives, which includes dexmedetomidine and midazolam. At the time of this authorization, FDA has determined that there is insufficient supply of the FDA-approved alternatives to fully meet the emergency need for Propofol-Lipuro 1% injectable emulsion for infusion in 100 mL vials.
[4] In the circumstances of this public health emergency, it would not be feasible to require healthcare providers to seek to limit Propofol-Lipuro 1% injectable emulsion for infusion only to be used for patients with suspected or confirmed COVID-19; therefore, this authorization does not limit use to such patients.
[5] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

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:

- Propofol-Lipuro 1% injectable emulsion for infusion will be used only to maintain sedation via continuous infusion in patients greater than 16 years old who require mechanical ventilation.[6]
- Propofol-Lipuro 1% injectable emulsion for infusion will be administered only by a licensed healthcare provider in an ICU setting.
- Propofol-Lipuro 1% injectable emulsion for infusion 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.
- Propofol-Lipuro 1% injectable emulsion for infusion will be used only in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

Product Description

Propofol-Lipuro 1% injectable emulsion for infusion is classified as a sedative hypnotic drug. The authorized product is an injectable emulsion in 100 mL vials containing 10 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.

Propofol-Lipuro 1% injectable emulsion for infusion is authorized for emergency use as described in the Scope of Authorization (Section II) with the following product-specific information to be made available to healthcare providers and patients, parents and caregivers, respectively, through B. Braun Melsungen's website at: https://www.bbraunusa.com/en/company/newsroom/covid19.html#,

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Propofol-Lipuro 1% injectable emulsion for infusion
- Fact Sheet for Patients, Parents, and Caregivers: Emergency Use Authorization (EUA) of Propofol-Lipuro 1% injectable emulsion for infusion

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 Propofol-Lipuro 1% injectable emulsion for infusion, 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 Propofol-Lipuro 1% injectable

[6] See footnote 4.

emulsion for infusion may be effective 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 Propofol-Lipuro 1% injectable emulsion for infusion (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), Propofol-Lipuro 1% injectable emulsion for infusion is authorized 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 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:

B. Braun Melsungen and Authorized Distributors[7]

A. B. Braun Melsungen and authorized distributor(s) will ensure that the authorized Propofol-Lipuro 1% injectable emulsion is distributed and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and healthcare providers consistent with the terms of this letter.

B. B. Braun Melsungen and authorized distributor(s) will ensure appropriate storage is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. B. Braun Melsungen authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving authorized Propofol-Lipuro 1% injectable emulsion for infusion. B. Braun Melsungen will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).

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

D. B. Braun Melsungen may request changes to this authorization, including to the authorized Fact Sheets for Propofol-Lipuro 1% injectable emulsion for infusion. Any request for changes to this EUA must be submitted to the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)/Office of Neuroscience/Office of New Drugs/Center for Drug Evaluation and Research (CDER). Such changes require appropriate authorization from FDA prior to implementation.[8]

E. B. Braun Melsungen may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of Propofol-Lipuro 1% injectable emulsion for infusion as described in this letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling of Propofol-Lipuro 1% injectable emulsion for infusion are prohibited. Should the Agency become aware of any instructional or educational materials that are inconsistent with the authorized labeling of Propofol-Lipuro injectable emulsion for infusion, the Agency will require B. Melsungen to cease distribution of such instructional or educational materials.

F. B. Braun Melsungen will report to FDA serious adverse events and all medication errors associated with the use of the Propofol-Lipuro 1% injectable emulsion for infusion that are reported to B. Braun Melsungen using either of the following options.

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

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: "Propofol-Lipuro 1% use for COVID-19 under Emergency Use Authorization (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.

[8] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. All changes to the authorization require review and concurrence from DAAP/CDER. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence also is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. B. Braun Melsungen will submit information to the Agency within three working days of receipt concerning significant quality problems with distributed drug product of Propofol-Lipuro 1%, that includes the following: (i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or (ii) Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet established specifications. If a quality problem affects unreleased product and may also implicate product(s) previously released and distributed, then the quality alert should be submitted for all impacted lots. B. Braun Melsungen will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, B. Braun Melsungen must recall them.

I. Braun Melsungen will manufacture Propofol-Lipuro 1% injectable emulsion for infusion to meet all quality standards, and per the manufacturing process and control strategy as detailed in B. Braun Melsungen's EUA request. B. Braun Melsungen will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without prior notification to and concurrence by the Agency as described in condition D.

J. B Braun Melsungen will list Propofol-Lipuro 1% injectable emulsion for infusion with a unique product NDC under the marketing category of Unapproved Drug- Other. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

K. Through a process of inventory control, B. Braun Melsungen and authorized distributor(s) will maintain records distribution of the authorized product (i.e., lot numbers, quantity, receiving site, receipt date).

L. B. Braun Melsungen and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

<u>Hospitals and Other Healthcare Facilities to Whom The Authorized Product Is Distributed and Healthcare Providers Administering the Authorized Product</u>

M. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of Propofol-Lipuro 1% injectable emulsion for infusion as described in the Scope of Authorization (Section II) under this EUA.

N. Healthcare facilities and healthcare providers receiving Propofol-Lipuro 1% injectable emulsion for infusion will track serious adverse events that are considered to be potentially attributable to the use of Propofol-Lipuro 1% injectable emulsion for infusion under this authorization and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports should state, "Propofol-Lipuro 1% injectable emulsion for infusion use for COVID-19 under Emergency Use Authorization (EUA)" at the beginning of the question "Describe Event" for further analysis.

O. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the products are administered consistent with the terms of this letter.

P. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized Propofol-Lipuro 1% injectable emulsion for infusion (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).

Q. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by B. Braun Melsungen and/or FDA. Such records will be made available to B Braun Medical, HHS, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising and Promotion

R. All descriptive printed matter, as well as advertising and promotional material, relating to the use of the Propofol-Lipuro 1% injectable emulsion for infusion 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.

S. No descriptive printed matter, as well as advertising or promotional material, relating to the use of the Propofol-Lipuro 1% injectable emulsion for infusion may represent or suggest that such products are safe or effective.

T. All descriptive printed matter, as well as advertising and promotional material, relating to the use of Propofol-Lipuro 1% injectable emulsion for infusion clearly and conspicuously shall state that:

- the Propofol-Lipuro 1% injectable emulsion for infusion is not FDA-approved, but has been authorized for emergency use by FDA 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

- the Propofol-Lipuro 1% injectable emulsion for infusion 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