Emergency Use Authorization (EUA) for Propofol-Lipuro 1%
Injectable Emulsion for Infusion
Center for Drug Evaluation and Research (CDER) Review

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number[1]	EUA-0096
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	B. Braun Melsungen AG 901 Marcon Boulevard Allentown, PA 18109 (610)266-0500
Manufacturer, if different from Sponsor	n/a
Submission Date	February 1, 2021
Receipt Date	February 1, 2021
OND Division / Office	Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP)/Office of Neurosciences (ON)
Reviewer Names/Disciplines	Renee Petit-Scott, MD, Clinical Reviewer Alla Bazini, MD, Associate Director for Anesthesiology Valerie Amspacher, PharmD, Quality Assessment Lead Katie Sokolowski, PhD, Pharmacology/Toxicology Reviewer Newton Woo, PhD, Pharmacology/Toxicology Team Leader Dan Mellon, PhD, Deputy Director Pharmacology/Toxicology Frank Wackes, PhD, Facilities Reviewer, OPMA CDR Tara Gooen Bizjak, Director Manufacturing Guidance and Policy Staff, OMQ Wei Qiu, PhD, Clinical Pharmacology Reviewer Yun Xu, PhD, Clinical Pharmacology Team Leader
Integrated Review Completion Date	3/12/21

[1] If a Pre-EUA is in existence at the time of the EUA request submission and has been assigned an EUA number, the EUA request should use the same EUA number and electronic archive file.

Proprietary Name	Propofol-Lipuro 1%
Established Name/Other names used during development	Propofol injectable emulsion for infusion
Dosage Forms/Strengths	1,000 mg/100 mL (10 mg/mL), Emulsion for continuous infusion
Therapeutic Class	Sedative-hypnotic
Intended Use or Need for EUA	To maintain sedation via continuous infusion in patients greater than 16 years old who require mechanical ventilation in the intensive care unit setting during the 2019 coronavirus disease (COVID-19) pandemic
Intended Population(s)	COVID-19 patients greater than 16 years old requiring sedation during intubation and mechanical ventilation in the intensive care unit setting
Product in the Strategic National Stockpile (SNS)	No
Distributor, if other than Sponsor	n/a

I. EUA Determination/Declaration

On February 4, 2020, Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act 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 a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV). The virus is now named SARS-CoV-2, which causes the illness COVID-19.

On the basis of this determination, the Secretary of Health and Human Services 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 FD&C Act, subject to the terms of any authorization issued under that section.

II. Recommendations

The Division of Anesthesiology, Addiction Medicine, and Pain Medicine, Office of Neuroscience, Office of New Drugs, CDER recommends EUA issuance.

B. EUA Communications

The EUA will be issued for Propofol-Lipuro 1% injectable emulsion for infusion 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 Intensive Care Unit (ICU) setting.[2]

C. Eligibility of the Product for an EUA

Serious or Life-threatening Disease or Condition:
Infection with the identified coronavirus, referred to as SARS-CoV-2, is capable of causing serious and life-threatening COVID-19. Many patients with COVID-19 develop pneumonia and reduced oxygenation, require intensive care, intubation, and mechanical ventilation for extended periods of time. Propofol is used extensively for intensive care unit (ICU) sedation in patients that are intubated and mechanically ventilated. Propofol reduces patient discomfort while intubated and mechanically ventilated, and optimizes mechanical ventilation in critically ill patients, particularly those requiring challenging ventilation protocols.

Evidence of Effectiveness and Benefit:Risk Determination:
Based on the scientific evidence available to FDA, it is reasonable to believe that the known and potential benefits of Propofol-Lipuro 1% injectable emulsion for infusion (Propofol-Lipuro 1%) outweigh the known and potential risks of the drug to maintain sedation via continuous infusion in patients greater than 16 years of age with suspect or confirmed COVID-19 who require mechanical ventilation in the intensive care unit.

Alternatives:
FDA-approved propofol, specifically manufactured in 100 mL vials, is currently in shortage due increased demand during the COVID-19 pandemic. FDA also assessed the supply of alternatives that are FDA approved to maintain sedation vi via continuous infusion in patients greater than 16 years of age who require mechanical ventilation in an ICU setting, 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% in 100 mL vials. Given the above, and based on the current public health need, FDA has limited this authorization to B. Braun's 100 mL vial of Propofol-Lipuro 1%. **T**

III. Proposed Use and Dosing of the Product Under the EUA

- Proposed use of Propofol-Lipuro 1%:
  - To maintain sedation of intubated and mechanically ventilated COVID-19 patients in an ICU setting.
- Proposed dosing regimen for use of Propofol-Lipuro 1%:

[2] As noted in the letter of authorization, in the circumstances of this public health emergency, it would not be feasible to authorize Propofol-Lipuro 1% injectable emulsion for infusion only to be used for patients with suspected or confirmed COVID-19; therefore, the authorization does not limit use to such patients. The scope of the authorization is supported by the review of the data and information available to FDA.

- Patients >16 years of age: The drug will be administered via continuous infusion. The dose will be adjusted according to the depth of sedation required. Usually satisfactory sedation is achieved by a continuous infusion with administration rates in the range of 0.3 to 4 mg/kg/h.

Limitations:

- 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.
- 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.

IV. Product Information (Dose Preparation and Administration)

Propofol has been marketed in the United States and European Union for decades. Propofol 1% (Diprivan®), manufactured by Fresenius Kabi, was approved in the United States in 1989. It is approved for sedation of intubated, mechanically ventilated patients. A Marketing Authorization certificate for Propofol-Lipuro 1% Emulsion was issued by the German Health Authority in 1999, and subsequently approved in other countries throughout the world for indications similar to Diprivan. Propofol-Lipuro 1% is not approved for use in the United States.

The following table compares Diprivan and Propofol-Lipuro 1% Formulations:

	U.S. DIPRIVAN	Propofol-Lipuro 1%
Formulation in mg/mL		
Propofol	10	10
Soybean Oil	100	(b) (4)
Glycerol	22.5	
Egg Phospholipid	12	
Sodium Hydroxide	pH 7-8.5	
Water	(b) (4)	
Disodium edetate (EDTA)	0.05	N/A
Sodium Oleate	N/A	(b) (4)
Medium Chain Triglycerides (MCT)	N/A	50
Sizes	10, 20, 50, 100 mL vials	100 mL vials*
Route of Administration	Intravenous	Intravenous

	U.S. DIPRIVAN	Propofol-Lipuro 1%
Indications	• induction of general anesthesia (patients ≥ 3 years of age) • maintenance of general anesthesia (patients ≥ 2 months of age) • initiation and maintenance of Monitored Anesthesia Care (MAC) sedation (adults only) • combined sedation and regional anesthesia (adults only) • Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients (adults only)	• induction and maintenance of general anesthesia in adults and children > 1 month • sedation for diagnostic and surgical procedures, alone or in combination with local or regional anesthesia in adults and > 1 month • sedation of ventilated patients >16 years of age in the intensive care unit
Storage	At or below 25°C; do not freeze	At or below 25°C; do not freeze
Exp Date	24 months	24 months
Packaging	Glass vial with rubber stopper and seal	Glass vial with rubber stopper and seal

*Propofol-Lipuro 1% 100 mL is the subject of this EUA request.
Source: EUA Interactive Review, B.Braun EUA Request.

There are three main differences between Diprivan 1% and Propofol-Lipuro 1%:

1. Propofol-Lipuro 1% contains a combination of medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs), whereas Diprivan 1% contains only LCTs.
2. Propofol-Lipuro 1% does not contain ethylenediaminetetraacetic acid (EDTA), whereas Diprivan 1% does.
3. Propofol-Lipuro 1% contains (b) (4) mg sodium oleate, which is not present in the Diprivan 1% formulation. Sodium oleate is listed in the FDA Inactive Ingredient Database, is not considered a novel excipient by the FDA, and its presence should not alter the safety profile.

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

Background Information on COVID-19

There are many types of human coronaviruses, including some that commonly cause mild upper-respiratory tract illness. The 2019 novel coronavirus, first identified in Wuhan China, and now identified as SARS-CoV-2, causes the disease named coronavirus disease 2019 (COVID-19). COVID-19 is a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death.

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. According to the WHO, more than 105 million confirmed

cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported globally as of February 7, 2021, including an estimated 2.3 million deaths. In the US, according to the Center for Disease Control and Prevention (CDC) as of February 7, 2021, approximately 26,761,047 cases of COVID-19 have been reported with an associated 460,582 deaths.

Per the CDC, COVID-19 reported in the United States has disproportionally affected the elderly. While approximately 14% of those infected with COVID-19 have been 65 years of age or older, this has accounted for approximately 81% of total deaths (https://covid.cdc.gov/covid-datatracker/#demographics accessed on 1/24/2021). These findings are similar to data from China, which indicated >80% of deaths occurred among persons aged ≥60 years (Wu *et al*, 2020).

Severe illness, defined as hospitalization, admission to the ICU, intubation or mechanical ventilation, or death, can occur in adults of any age with COVID-19. Adults of any age with certain underlying comorbidities or conditions such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, type 2 diabetes, pregnancy, and immunocompromised states are at increased risk for severe illness from the virus that causes COVID-19 (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-withmedical-conditions.html).

The respiratory presentation in adolescents has been similar to that in adults. The disease is typically milder in children, but a small proportion have experienced severe disease that requires treatment in an ICU and prolonged mechanical ventilation (Götzinger *et al*, 2020).

Therapeutic Alternatives for ICU sedation of COVID-19 patients that are intubated and mechanically ventilated.

- Approved products indicated for sedation of intubated and mechanically ventilated patients in the ICU setting include propofol, dexmedetomidine, and midazolam.
- See section II.C of this memorandum for FDA's assessment on the availability of FDA approved propofol products, including FDA-approved alternatives to Propofol-Lipuro 1% injectable emulsion for infusion.

Description of the proposed EUA product's (Propofol-Lipuro 1%) potential to address an unmet need of administrating sedation in the ICU setting for intubated and mechanically ventilated COVID-19 patients.

- Propofol-Lipuro 1% has been approved and marketed in the European Union since 1999. The approved indications in the European Union for Propofol-Lipuro 1% are similar to the U.S. Diprivan 1% indications and include sedation in patients over 16 years of age in the intensive care unit. The 100 mL presentation proposed for this EUA is currently marketed in Europe and other countries around the world. Diprivan is approved as a 100 mL presentation in the U.S.

- B. Braun Medical, Inc. (B. Braun) is proposing Propofol-Lipuro 1% (100 mL size) to enable immediate utilization of existing manufacturing capacity to maximize the amount of propofol available for ICU sedation during the COVID-19 pandemic. B. Braun has adequate raw materials to increase the quantity of propofol manufactured.

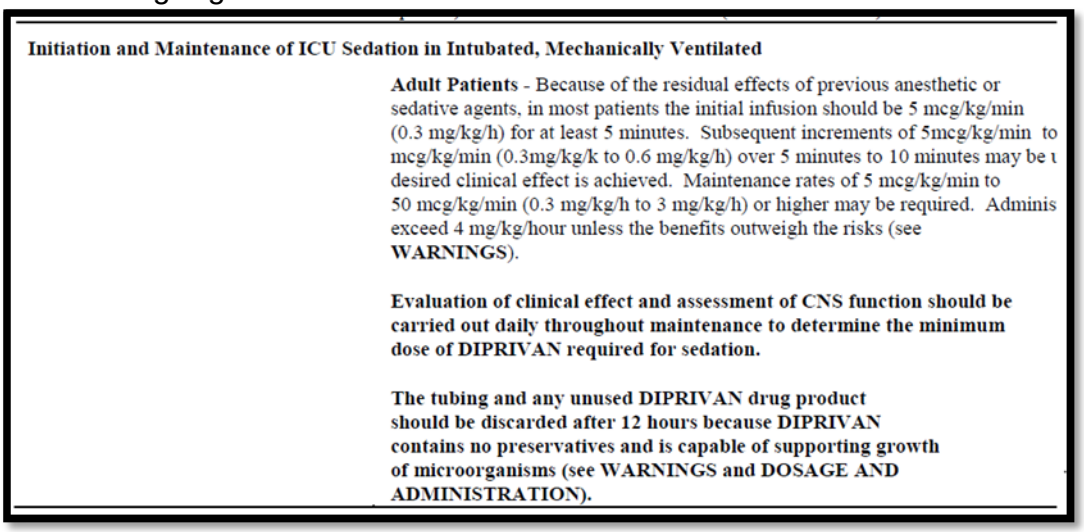
VI. Related Regulatory Submission(s)

- Related NDA to the EUA product, Propofol-Lipuro 1%
  - NDA 019627, Diprivan 1%
    - Approved: October 2, 1989
    - Sponsor: Fresenius Kabi USA, LLC
    - Indications:

Indication	Approved Patient Population
Initiation and maintenance of Monitored Anesthesia Care (MAC) sedation	Adults only
Combined sedation and regional anesthesia	Adults only (see **PRECAUTIONS**)
Induction of General Anesthesia	Patients ≥ 3 years of age
Maintenance of General Anesthesia	Patients ≥ 2 months of age
Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients	Adults only

Source: Diprivan Prescribing Information, Table 3.

    - Dosing regimen:



Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated

Adult Patients - Because of the residual effects of previous anesthetic or sedative agents, in most patients the initial infusion should be 5 mcg/kg/min (0.3 mg/kg/h) for at least 5 minutes. Subsequent increments of 5mcg/kg/min to mcg/kg/min (0.3mg/kg/k to 0.6 mg/kg/h) over 5 minutes to 10 minutes may be u desired clinical effect is achieved. Maintenance rates of 5 mcg/kg/min to 50 mcg/kg/min (0.3 mg/kg/h to 3 mg/kg/h) or higher may be required. Adminis exceed 4 mg/kg/hour unless the benefits outweigh the risks (see **WARNINGS**).

Evaluation of clinical effect and assessment of CNS function should be carried out daily throughout maintenance to determine the minimum dose of DIPRIVAN required for sedation.

The tubing and any unused DIPRIVAN drug product should be discarded after 12 hours because DIPRIVAN contains no preservatives and is capable of supporting growth of microorganisms (see WARNINGS and DOSAGE AND ADMINISTRATION).

Source: Diprivan Prescribing Information.

    - Dosage forms:

HOW SUPPLIED:

DIPRIVAN (propofol) Injectable Emulsion, USP Vials

Product No.	NDC No.	Strength	
260929	63323-269-29	200 mg per 20 mL (10 mg per mL)	20 mL ready-to-use single-patient infusion vial in packages of ten.
260950	63323-269-50	500 mg per 50 mL (10 mg per mL)	50 mL ready-to-use single-patient infusion vial in packages of twenty.
260965	63323-269-65	1,000 mg per 100 mL (10 mg per mL)	100 mL ready-to-use single-patient infusion vial in packages of ten.

Source: Diprivan Prescribing Information.

- Duration (verbatim form Diprivan Label, Warnings Section):
  Use of DIPRIVAN infusions for both adult and pediatric ICU sedation has been associated with a constellation of metabolic derangements and organ system failures, referred to as Propofol Infusion Syndrome, that have resulted in death. The syndrome is characterized by severe metabolic acidosis, hyperkalemia, lipemia, rhabdomyolysis, hepatomegaly, renal failure, ECG changes* and/or cardiac failure. The following are the risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high dosages of one or more of the following pharmacological agents: vasoconstrictors, steroids, inotropes and/or prolonged, high-dose infusions of propofol (greater than 5 mg/kg/h for greater than 48 h). The syndrome has also been reported following large-dose, short-term infusions during surgical anesthesia. In the setting of prolonged need for sedation, increasing propofol dose requirements to maintain a constant level of sedation, or onset of metabolic acidosis during administration of a propofol infusion, consideration should be given to using alternative means of sedation.

  **Coved ST segment elevation (similar to ECG changes of the Brugada syndrome).*

- Related Products:

Proprietary Name	Appl. No.	Route	Strength	Applicant Holder	Approval Date
DIPRIVAN*	N019627	Injection	10 mg/mL	FRESENIUS KABI USA, LLC	Jun 11, 1996
Propofol	A205067	Injection	10 mg/mL	DR REDDYS LABORATORIES INC	Nov 15, 2018
Propofol	A077908	Injection	10 mg/mL	HOSPIRA INC	Mar 17, 2006
Propofol	A205576	Injection	10 mg/mL	INNOPHARMA LICENSING LLC A SUB OF PFIZER INC	Sep 16, 2020
Propofol	A075102	Injection	10 mg/mL	SAGENT PHARMACEUTICALS INC	Jan 4, 1999

Proprietary Name	Appl. No.	Route	Strength	Applicant Holder	Approval Date
Propofol	A205307	Injection	10 mg/mL	WATSON LABORATORIES INC	Dec 22, 2015
Propofol	A074848	Injection	10 mg/mL	WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD	April 12, 2005

*Reference Listed Drug. All products available in 20, 50, and 100 mL vial presentations.
Source: EUA Interactive Review, Table 2 (p. 18-19), B.Braun EUA Request.

VII. Summary of Clinical Data

Propofol 1% (Diprivan) was approved in the United States in 1989. Its safety and efficacy profiles are well established. Propofol-Lipuro 1% is approved in Europe, as well as many other international countries outside of the United States. The global sales history reported by B. Braun for Propofol-Lipuro 1% from 2017 to 2019 includes the sale of (b) (4) units, and includes all vial presentations (i.e., 20 mL, 50 mL, and 100 mL) (Post-Marketing Surveillance Data on Propofol-Lipuro 1%, Sol. No. 0598, Applicant's submission, EUA-96, February 1, 2021).

The presence of MCTs in a 1:1 combination with LCTs in Propofol-Lipuro 1% is different from the Diprivan formulation, which contains only LCTs. Prolonged intravenous infusion of high-dose MCTs to pregnant rabbits has been reported to increase the risk for neural tube defects, including anencephaly, rachischisis, and exencephaly. During review of NDA 207929, a marketing application submitted on December 7, 2015, by B. Braun for Propofol-0590, a product similar to Propofol-Lipuro 1% with preservative, the Division concluded that these nonclinical data do represent a true signal; however, the clinical relevance is uncertain. It seems likely that the described neural tube defects would occur in humans only after high levels of exposure in early pregnancy. The Applicant did not address the risk of potential neural tube defects in the EUA submission; however, mitigation strategies include routine pregnancy testing and administration of Propofol-Lipuro 1% to pregnant women only if there are no other FDA-approved products available to maintain sedation for COVID-19 patients requiring mechanical ventilation.

NDA 207929 received a Complete Response Letter (CRL) on January 6, 2017. The identified clinical deficiencies were related to (b) (4) .

Subsequent to the CRL, two post-action meetings were held with the Applicant. In a meeting request packet, received February 21, 2019, synopses for two clinical studies, one in adults and one in pediatric subjects, evaluating the safety of administration of MCTs during longer surgical procedures and ICU sedation, were submitted. The Applicant proposed to evaluate Propofol-Lipuro 1% compared to Diprivan, and to conduct the studies in Europe. The Agency advised the Applicant that the acceptability of utilizing Propofol-Lipuro 1%, not approved in the United

States, to generate safety data to support approval of another NDA product, Propofol-0590, would require additional internal discussions. Subsequent to the meeting held on June 24, 2019, there have been no communications with the Applicant aside from two annual NDA extension requests (2020 and 2021).

In the NDA (207929) submission, B. Braun provided results from a bioequivalence study, HC-G-H-1308, comparing Propofol-0590 to the listed drug, Diprivan. In the Applicant's Response document submitted with the EUA Request, B. Braun states the following;

> *With regard to the clinical study conducted under the mentioned NDA, we like to state that this bioequivalence study (HC-G-H-1308, demonstrating bioequivalence between Propofol-0590 and Diprivan 1%) can be used to support the EUA product as well for the following reasons:*
>
> – *Propofol-0590 and the EUA product are essentially the same - except for EDTA, whereas Propofol-0590 contains* (b) (4) *mg per mL of EDTA and the EUA product is EDTA-free*
> – *It is known, that EDTA does not impact the pharmacokinetics of propofol Consequently, it can be concluded that the EUA product is bioequivalent to Diprivan 1%.*

The results of this study indicated that single intravenous doses of Propofol-0590 and Diprivan at 2 mg/kg bodyweight in adults were well-tolerated. The safety and efficacy profiles of the two formulations were comparable. There were no serious or severe adverse events and no subject was discontinued from the study due to an adverse event. The incidence of injection site reactions was lower in subjects who received Propofol-0590 compared to those who received Diprivan.

Sources of clinical data:

- Summary Review for Regulatory Action and the Cross-Discipline Team Leader Review, NDA 207929.
- Applicant Response Document, Applicant's EUA Request, EUA-96.
- EUA Interactive Review, Applicant's EUA Request, EUA-96.

VIII. Human Clinical Efficacy

Evidence of Effectiveness

Propofol is a sedative-hypnotic agent. Diprivan 1% Injectable Emulsion, 10 mg/mL, (NDA 019627) was approved on October 2, 1989, and has the following indications:

Indication	Approved Patient Population
Initiation and maintenance of Monitored Anesthesia Care (MAC) sedation	Adults only
Combined sedation and regional anesthesia	Adults only (see **PRECAUTIONS**)
Induction of General Anesthesia	Patients ≥ 3 years of age
Maintenance of General Anesthesia	Patients ≥ 2 months of age
Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients	Adults only

Source: Diprivan Prescribing Information, Table 3.

Propofol is used as a sedative for critically ill patients in the ICU who require intubation and mechanical ventilation. In critically ill patients that develop respiratory distress or respiratory failure, propofol is used to provide patient comfort and to optimize mechanical ventilation, thereby, improving oxygenation and ventilation while other therapies are initiated to treat the underlying disease or sequalae of the disease. Many mechanically ventilated COVID-19 patients require challenging ventilation protocols, including prone positioning, and, therefore, higher doses of propofol to maintain adequate sedation. In addition, some patients require prolonged periods of mechanical ventilation, i.e., greater than 10 days. As a result, propofol has been identified as a critical and medically necessary drug and the supply of the drug has been in shortage status since April 10, 2020.

The only significant differences between Diprivan and Propofol-Lipuro 1% include lack of a preservative agent and the presence of MCTs in Propofol-Lipuro 1%, and the only difference between Propofol-Lipuro 1% and Propofol-0590, the proposed NDA product, is the lack of a preservative agent. Therefore, based on results from the bioequivalence study, HC-G-H-1308, comparing Propofol-0590 and Diprivan, the Applicant concludes that Propofol-Lipuro 1% is also bioequivalent to Diprivan.

It does not appear there are published data reporting differences in efficacy between Diprivan and Propofol-Lipuro 1%. As noted above, information from NDA 207929 suggests that higher Propofol-0590 dosing may be required for induction of anesthesia in pediatric patients; however, this EUA will be limited to use in patients older than 16 years of age. After review of the data submitted for the last renewal of the Marketing Authorization in Europe, the Reference Member State (RMS) indicated that the renewal could be granted with unlimited validity. The RMS also reported that the efficacy of propofol has been established over many years, with widespread clinical experience, and that, “no information giving any hint for a lack of efficacy is available”. No additional efficacy data were provided by the Applicant.

Based upon the extensive clinical experience with Diprivan 1% and the fact that Propofol-Lipuro 1% has been marketed in many non-U.S. countries since 1999, it is reasonable to conclude that it is scientifically plausible that Propofol-Lipuro 1%, with the same API as Diprivan, will also be efficacious in the indicated population, adult patients with COVID-19 requiring mechanical ventilation.

IX. Human Clinical Safety

Key safety considerations for all propofol formulations (adapted from the EUA Interactive Review and Summary of Product Characteristics):

- Off-label use of propofol for ICU sedation in pediatric patients has been associated with a constellation of metabolic derangements and organ failure which may be fatal. Based on these life-threatening reactions, propofol administration for patients 16 years of age and younger is contraindicated. This EUA will be limited to patients older than 16 years of age.
- Propofol Infusion Syndrome (PRIS) is a constellation of symptoms, including metabolic acidosis, rhabdomyolysis, hyperkalemia, hepatomegaly, renal failure, hyperlipidemia, cardiac arrhythmia, Brugada-like ECG pattern, and rapidly progressive cardiac failure which develops in patients receiving propofol, including short-term infusions during surgical anesthesia. Doses above 4 mg/kg/h are not recommended. Risk factors for the development of PRIS include decreased oxygen delivery to tissues, serious neurological injury, and/or sepsis, and administration of one or more vasopressor, steroid, inotrope, and/or propofol. Providers should be aware of the risk factors for PRIS and immediately discontinue propofol when signs and/or symptoms develop.
- Hypotension is commonly reported after administration of propofol, and may require treatment, including reduction in the infusion rate. Concomitant administration of other central nervous system depressants, such as inhalational anesthetic agents, may potentiate the depressant effects of propofol. Patients receiving propofol must be constantly monitored by trained anesthesia professionals.
- Dose-dependent respiratory depression has been reported with administration of propofol. Cardiorespiratory depression can occur at high blood concentrations resulting from rapid increases in infusion rates. Only providers trained in anesthesia or critical care should administer propofol, patients receiving propofol should be adequately monitored, and resuscitative equipment must be readily available.
- Patients with mitochondrial disease who receive anesthesia or ICU care or undergo surgery may be at risk of exacerbations. The early presentations of mitochondrial disease exacerbation and propofol infusion syndrome may be similar.
- Patients with a history of epilepsy may be at risk of seizures during propofol administration or the recovery phase.

<u>Advisory Statements Regarding ICU Management (verbatim from the Summary of Product Characteristics)</u>

- Use of propofol for ICU sedation has been associated with a constellation of metabolic disturbances and organ system failures that may result in death. Reports have been received of combinations of the following: Metabolic acidosis, Rhabdomyolysis, Hyperkalaemia (*sic*), Hepatomegaly, Renal failure, Hyperlipidaemia (*sic*), Cardiac arrhythmia, Brugada-type ECG (elevated ST-segment and coved T-wave) and rapidly progressive Cardiac failure usually unresponsive to inotropic supportive treatment. Combinations of these events have been referred to as the Propofol Infusion Syndrome. These events were mostly seen in patients with serious head injuries and children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit. The following appear to be the major risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high dosages of one or more of the following pharmacological agents - vasoconstrictors, steroids, inotropes and/or propofol (usually at dose rates greater than 4 mg/kg/h for more than 48 hours).
- It is recommended that blood lipid levels should be monitored if propofol is administered to patients thought to be at particular risk of fat overload. Administration of propofol should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is receiving other intravenous lipid concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the propofol formulation; 1.0 mL of Propofol-Lipuro contains approximately 0.1 g of fat.

<u>Adverse Drug Reactions (from the Summary of Product Characteristics)</u>
The following are the commonly reported adverse reactions:

- Headache during recovery phase
- Bradycardia; serious bradycardia is rare with isolated reports of progression to asystole
- Hypotension, occasionally requiring intravenous fluid administration and decrease rate of propofol infusion
- Transient apnea during induction
- Nausea and vomiting during recovery phase
- Local pain on induction

<u>Additional Safety Concerns</u>

- As previously discussed, Propofol-Lipuro 1% contains a combination of MCTs and LCTs, and Diprivan contains only LCTs. Nonclinical data do suggest there is a risk of neural tube defects with prolonged infusions of high-dose MCTs. This risk can be mitigated by routine pregnancy testing and administration of Propofol-Lipuro 1% to pregnant women if only there are no other FDA-approved products available to maintain sedation for COVID-19 patients requiring mechanical ventilation.

- Propofol-Lipuro 1% does not contain an antimicrobial preservative and, therefore, can support growth of microorganisms. The Summary of Product Characteristics states the following:
    - Propofol-Lipuro 1% must be drawn up aseptically into a sterile syringe or an infusion set immediately after breaking the vial seal.
    - Administration must not be delayed.
    - Aseptic technique must be maintained for both Propofol-Lipuro 1% and the infusion equipment throughout the infusion period.
    - Any medicinal products or fluids added to a running Propofol-Lipuro 1% infusion must be administered close to the cannula site.
    - Propofol-Lipuro 1% must not be administered via infusion sets with microbiological filters.
    - The contents of one vial of Propofol-Lipuro 1% and any syringe containing Propofol-Lipuro 1% are for single use in one patient.
    - A single infusion of Propofol-Lipuro 1% must not exceed 12 hours. After 12 hours, both the reservoir of Propofol-Lipuro 1% and the infusion tubing must be discarded.

Based on review of the Periodic Safety Update Report (PSUR) from 2012 through 2017, and the Post-Marketing Surveillance Data from 2017 through 2019 for Propofol-Lipuro 1%, it does not appear there were any new adverse reactions reported that were not also included in the Diprivan Prescribing Information. However, after review of the PSUR in 2018, the Lead Member of State of the PSUR Single Assessment Procedure recommended strengthening the warning regarding propofol infusion syndrome in Section 4.4 of the Summary of Product Characteristics. This change has been incorporated into the summary document. No changes or updates to the package leaflet were recommended.

Adverse Event Profile for Propofol-Lipuro 1% is available in the Summary of Product Characteristics.

Release and Shelf-Life Specification for Propofol-Lipuro 1%

Test	Release specification	Shelf life specification
General and Special Characteristics		
Extractable volume	not less than the nominal volume of the container	-
Appearance	a white, milky oil-in-water emulsion	a white, milky oil-in-water emulsion
Odor	weakly phenol-like	weakly phenol-like
Identity		
Soya oil	complies	-
Medium-chain triglycerides	complies	-
Egg lecithin	complies	-
Glycerol	complies	-

Propofol UV spectrum	maximum absorption: (b) (4) nm shoulder near (b) (4) nm	-
Purity Tests		
pH	(b) (4)	
Microscopic assessment		
(b) (4)		
Impurities		
(b) (4)		
Sterility		
Bacterial endotoxins		
Assay		
Propofol	(b) (4)	
Additional parameters tested since 2015		
Lysophosphatidylcholine (LPC)	-	(b) (4)
Subvisible particles Small volume parenterals (≤ 100 ml per container)	-	
PFAT5	-	
Particle Size (PCS)	-	

*these parameters were not tested at all stability time points, but at least start and end points

X. Specific Populations

Special Patient Groups

Cardiac, respiratory, renal, or hepatic insufficiency, and hypovolemia

As with other intravenous anesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolemic or debilitated patients. Propofol clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce propofol clearance.

Propofol lacks vagolytic activity and has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of an anticholinergic agent before induction or during maintenance of anesthesia should be considered, especially in situations where vagal tone is likely to predominate or when propofol is used in conjunction with other agents likely to cause bradycardia.

Epilepsy
When Propofol-Lipuro 1% is administered to patients with a history of epilepsy, there may be a risk of seizure. Although several studies have demonstrated efficacy in treating status epilepticus, administration of propofol in epileptic patients may also increase the risk of seizure. Epileptiform movements, including convulsions and opisthotonos during induction, maintenance, and recovery have been reported. Before sedation and anesthesia of an epileptic patient, it should be checked that the patient has received the antiepileptic treatment.

Use of propofol is not recommended with electroconvulsive therapy.

Patients with disorders of fat metabolism
Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.

It is recommended that blood lipid levels should be monitored if propofol is administered to patients thought to be at particular risk of fat overload. Administration of propofol should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is receiving other intravenous lipid concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the propofol formulation.

Patients with a high intracranial pressure
Patients with raised intra-cranial pressure (ICP) should be given appropriate treatment to support the cerebral perfusion pressure. Treating physicians are reminded, if possible, not to exceed the dosage of 4 mg/kg/h.

Mitochondrial disease
Caution should be taken when treating patients with mitochondrial disease. These patients may be susceptible to exacerbations of their disorder when undergoing anesthesia, surgery, and ICU care. Maintenance of normothermia, provision of carbohydrates, and good hydration are recommended for such patients. The early presentations of mitochondrial disease exacerbation and of the propofol infusion syndrome may be similar.

Pregnant and Breast-feeding patients
The safety of propofol during pregnancy has not been established. Studies in animals have shown reproductive toxicity. Propofol should not be given to

pregnant women except when absolutely necessary. Propofol crosses the placenta and can cause neonatal depression.

Nonclinical data from studies evaluating propofol formulations containing MCTs, such as Propofol-Lipuro 1%, indicate a risk of neural tube defects. These formulations are, therefore, recommended for use in pregnant women only if there are no other FDA-approved products available to maintain sedation for COVID-19 patients requiring mechanical ventilation.

Studies of breast-feeding mothers showed that small quantities of propofol are excreted in human milk. Women should, therefore, not breastfeed for 24 hours after administration of propofol. Milk produced during this period should be discarded.

Pediatric patients
Propofol must not be used in patients of 16 years of age or younger for sedation for intensive care as the safety and efficacy of propofol for sedation in this age group have not been demonstrated.

XI. Human Clinical Pharmacology

B. Braun's Propofol-Lipuro 1% Emulsion has the same concentration of propofol compared to FDA- approved Diprivan 1%. No comparative bioavailability study was conducted between Propofol-Lipuro 1% and Diprivan 1%. As previously mentioned, B. Braun submitted NDA 207929 for Propofol-0590, and received a complete response based primarily on nonclinical deficiencies. The only difference between B. Braun's Propofol-0590 and Propofol-Lipuro 1% is that Propofol-0590 contains EDTA and Propofol-Lipuro 1% is EDTA-free. B. Braun conducted a bioequivalence study, HC-G-H-1308, comparing Propofol-0590 and Diprivan 1%, and submitted the results in their NDA (207929). Study HC-G-H-1308 was reviewed and it was concluded that bioequivalence was demonstrated between Propofol-0590 and Diprivan 1%. In the EUA package, the Applicant submitted information from the published literature indicating that the addition of EDTA in Propofol-0590 does not alter the pharmacokinetics of propofol. Although no comparative bioavailability study was conducted between Propofol-Lipuro 1% and Diprivan 1%, it is reasonable to conclude that Propofol-Lipuro 1% would be bioequivalent to Diprivan 1% because of the demonstrated bioequivalence between Propofol-0590 and Diprivan 1%, and the lack of an effect of EDTA on the pharmacokinetic profile of propofol.

Pharmacodynamic Properties

Mechanism of action/Pharmacodynamic effects
Propofol (2,6-diisopropylphenol) is a short-acting general anesthetic agent with a rapid onset of action. Depending on the rate of injection, the time to induction of anesthesia is between 30 and 40 seconds. The duration of action after a single bolus administration is short and lasts, depending on the metabolism and elimination, 4 to 6 minutes.

Clinical efficacy and safety

- With the recommended dosing schedule, clinically relevant accumulation of propofol after repeated bolus injection or after infusion has not been observed. Patients recover consciousness rapidly.
- Bradycardia and hypotension occasionally occur during induction of anesthesia, and may be due to lack of the vagolytic activity of propofol. These changes in hemodynamics generally normalize during maintenance of anesthesia.

Pharmacokinetic Properties

Distribution

Propofol is 98% bound to plasma proteins. Following intravenous administration, the pharmacokinetics of propofol can be described by a 3-compartment model.

Biotransformation / Elimination

Propofol is extensively distributed and rapidly cleared from the body (total body clearance: 2 liters/minute). Clearance occurs by metabolic processes, mainly in the liver where it is blood flow dependent, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.

After a single dose of 3 mg/kg intravenously, propofol clearance/kg body weight increased with age as follows: Median clearance was considerably lower in neonates < 1 month old (n=25) (20 ml/kg/min) compared to older children (n=36, age range 4 months – 7 years). Additionally, inter-individual variability was considerable in neonates (range 3.7 - 78 mL/kg/min). Due to this limited trial data that indicates a large variability, no dose recommendations can be given for this age group.

Median propofol clearance in older aged children after a single 3 mg/kg bolus was 37.5 ml/min/kg (4 - 24 months) (n=8), 38.7 ml/min/kg (11 - 43 months) (n=6), 48 ml/min/kg (1-3 years) (n=12), 28.2 mL/min/kg (4-7 years) (n=10) as compared with 23.6 ml/min/kg in adults (n=6).

XII. Nonclinical Data to Support Safety

The proposed drug product is the same 1% propofol concentration as Diprivan but is slightly different in formulation as the proposed product contains medium chain triglycerides (MCT) and lacks EDTA. However, these differences do not alter the pharmacology or toxicology profile of the drug product with the possible exception of the potential effects of MCT on reproductive and developmental endpoints which is further discussed below. Although nonclinical data to support the safety of the BBraun propofol product was not provided in the EUA submission, the proposed dose, duration, and intravenous route of administration is within labeled use of Diprivan.

MCT have been used in U.S. FDA-approved intravenous drug products with a maximum daily intake of (b) (4) mg (parenteral nutrition product (NDA 208399). A recent review of MCT conducted by the U.S. FDA did identify published studies suggesting the potential for neural tube defects when a 3:1 mixture of MCT and long chain triglycerides (LCT) were infused via intravenous route daily to pregnant rabbits over the period of organogenesis in the presence of maternal toxicity (Henwood et al., 1997). The clinical significance of these findings is not clear; however, the effects may be the results of ketoacidosis secondary to metabolic disturbances. Because it is not yet clear if the 1:1 mixture of MCT:LCT infusions are associated with adverse developmental effects, this product should be used in pregnant women only if there are no other FDA-approved products available and the clinical benefit is warranted.

Based on submitted CMC information, lysophosphatidylcholine (LPC), which is an impurity arising from the excipient egg phospholipids, is associated with a specification of (b) (4) g/L, which appears to be higher than Diprivan. LPC is a naturally occurring metabolic product of phosphotidylcholine in the human body and is recognized as an important homeostatic mediator involved in vascular inflammation. As such, the body has mechanisms to control levels of LPC, such as albumin binding and rapid hepatic clearance. The maximum amount of LPC administered during maintenance infusion for general anesthesia or ICU sedation is not expected to significantly alter endogenous levels of LPC. Given the baseline blood levels of LPC in human plasma are not expected to be significantly altered and the clinical experience in Europe with the proposed product, the increased specification of LPC compared to Diprivan does not raise concerns for the safety use of the BBraun 1% propofol drug product in humans.

To address the safety of the container closure system (CCS), this EUA submission contained an Applicant Response Document which contained the DMF (b) (4) reference for the rubber stopper, an expert statement, and a risk assessment to justify the leachables from the container closure system. While the submitted documentation does not completely address the safety of the CCS adequately, there are FDA-approved products using the proposed CCS. Given the (b) (4) rubber formula and similar (b) (4) coating have been used in other FDA-approved propofol products, the submitted leachables data do not raise significant safety concerns with the container closure system.

XIII. Nonclinical Data to Support Efficacy

N/A

XIV. Supply Information

The Applicant states that the emergency supply of Propofol-Lipuro 1% will help address the shortage of propofol injectable emulsions and "expand domestic readiness within the United States and its territories by increasing sedation capabilities for critically ill patients that require mechanical ventilation during the COVID-19 pandemic and public health emergency in the United States." In order to address the current emergency needs, the EUA will be limited to authorizing the 100 mL vial presentation of Propofol-Lipuro 1% at this time.

B. Braun has allocated maximum (b) (4) units per month of 100 mL vials of Propofol-Lipuro 1% in its supply chain planning for the 2021 calendar year, beginning February 2021. B. Braun has indicated they are also prepared to supply approximately (b) (4), 50 mL vials should the Agency consider expanding the scope of the EUA. Under the EUA, (b) (4) will assist the Applicant with Propofol-Lipuro 1% distribution.

- The Applicant has indicated that an average size adult patient, weighing 75 kg, would require approximately 54 mL to 720 mL (average 300 mL) per day for sedation during mechanical ventilation. Therefore, on average, a single adult patient would require three 100 mL vials of Propofol-Lipuro 1%.
- One hundred thousand vials of Propofol-Lipuro 1% would maintain sedation during mechanical ventilation for approximately 33,333 patient days. For a course of sedation lasting seven days, the amount of Propofol-Lipuro 1% provided by B. Braun would allow for sedation of an additional 4,762 ICU patients per month.

XV. Chemistry, Manufacturing, and Controls Information

SEE ATTACHED ADDENDUM

- The sponsor of this EUA, B. Braun Medical Inc. is also the applicant for NDA 207929. The CMC recommendation for NDA 207929 is for approval. The formulation in both applications is identical except the formulation in the NDA includes Edetate Disodium (EDTA). EDTA is not present in the formulation subject to this EUA application.
- The drug substance is manufactured at the same site in both The EUA and NDA applications. This provides enough information to support the drug substance in this EUA.
- The drug product in the EUA is manufactured at a different site from the drug product in the NDA.
- The sponsor has provided batch analysis for one batch of product made in October 2020. Additionally, 3 batches of stability data are provided showing adequate stability of the drug product out to 24 months. This is adequate to support use of the drug product in this EUA.
- The excipients include: Soybean oil, medium chain triglycerides, egg phospholipids, glycerol, sodium oleate, water for injection. Certificates of analysis for these excipients in NDA 207929 provide adequate information to support their use in this drug product.

- The sponsor confirmed that the (b) (4) process for the drug product is identical to the (b) (4) process that was previously reviewed in NDA 207929 and was found acceptable from a product quality microbiology perspective.

XVI. Manufacturing Site Inspections

Table 4: Manufacturing Sites

Mfg. Site Identifier	Drug Substances/ Intermediates/ Drug Product/ Testing/Labeler/ Packager	Location (US and Non-US)	Associated NDA, BLA, or IND	Commercial Sponsor/ Applicant	Inspection Dates	GMP Status (if known)
(b) (4)	DS Mfg.	(b) (4)	DMF (b) (4)	(b) (4)	(b) (4)	Acceptable *1
B. Braun Melsungen FEI 3002806469	DP Mfg.	Non-US (Germany)	NDA 207929 IND 108521	B. Braun	May 2019 (Health Canada) & Sep 2016 (FDA)	Acceptable *2

Note *1: Declaration was provided that (b) (4) site complies with current good manufacturing practice requirements of U.S. Federal Food, Drug, and Cosmetic Act Section 501(a)(2)(B).

Note *2: Declaration was provided that B. Braun site complies with EU GMP and that the drug product follows European Pharmacopoeia; and that site complies with current good manufacturing practice requirements of U.S. Federal Food, Drug, and Cosmetic Act Section 501(a)(2)(B).

Based on FDA's evaluation of the manufacturing process and control strategy, and the listed facilities, FDA considers the following condition(s) to the authorization as necessary to protect the public health[3]:

- Braun Medical 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 Medical's EUA request. B. Braun Medical 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

[3] See the evaluation documented in OMQ's EUA Recommendation Memo in CMS Case# 613443 dated March 4, 2021 and OPMA's EUA Manufacturing Assessment Memo associated with EUA 0096 dated March 4, 2021.

as described in the corresponding condition detailing the process by which B. Braun Medical may request changes to the authorization (i.e., condition D)

- All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of the Federal Food, Drug, and Cosmetic Act Section 501(a)(2)(B).
- B. Braun Medical 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 Medical 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 Medical must recall them.
- B Braun 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.

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

Since the initial confirmed case of COVID-19 in the United States on January 20, 2020 (Holshue *et al.*, 2020), the number of cases has risen to over 26 million with more than 460,000 deaths (World Health Organization Coronavirus Disease [COVID-19] Dashboard, February 7, 2021). Due to the increasing number of cases of COVID-19, there is an increased demand for drugs used for sedation of intubated and mechanically ventilated patients in ICU settings. This increased demand has impacted the availability of the FDA-approved sedative drug products, including propofol, dexmedetomidine, and midazolam, such that there is an insufficient supply of the FDA-approved propofol products, and FDA-approved alternatives, to fully meet the emergency need. In addition to the possibility of prolonged sedation requirements, it appears that COVID-19 patients tend to require larger doses of sedative medications to ensure adequate comfort and tolerance of challenging mechanical ventilation protocols, including prone positioning. Therefore, there is a critical need to increase the availability of additional propofol products in the United States.

An EUA for another propofol product, Fresenius Propoven 2%, manufactured by Fresenius Kabi, USA, LLC, was granted on May 8, 2020, on the basis of critical sedation drug shortages. This propofol product is double the concentration of both

the listed drug, Diprivan 1%, and Propofol-Lipuro 1%. Drug product labeling, and specially-made graphic wall charts and vial stickers alert the prescriber to the higher propofol concentration in an attempt to mitigate the risk of drug overdosage. Fresenius Propoven 2% also contains a combination of MCTs and LCTs and is not recommended for use in pregnant women unless other approved products are unavailable for sedation during mechanical ventilation due to COVID-19. There have been no apparent safety signals identified subsequent to granting the EUA request. Refer to the EUA Summary Review, dated May 8, 2020, for additional information regarding the benefits and risk of Fresenius Propoven 2% administration for sedation during mechanical ventilation of COVID-19 patients.

Temporary importation of Fresenius Propoven 1%, also manufactured by Fresenius Kabi, was permitted during previous propofol shortages in the United States. Fresenius Propoven 1% and Propofol-Lipuro 1% are similar in that they are the same concentration as the listed drug, Diprivan 1%, and they both contain a combination of MCTs and LCTs, similar to Fresenius Propoven 2%. There were no apparent safety signals identified during the time periods of importation of the MCT/LCT formulation of Fresenius Propoven 1% emulsion.

Although the safety of the intravenous MCT/LCT combination formulation can be supported by prior human experience, a recent review of the safety of MCTs conducted by the Agency identified studies in the published literature suggesting the potential for the development of neural tube defects. Specifically, when a 3:1 mixture of MCTs and LCTs was infused via intravenous route daily to pregnant rabbits over the period of organogenesis in the presence of maternal toxicity (Henwood *et al*., 1997), neural tube defects such as anencephaly, rachischisis, and exencephaly were observed. The clinical significance of these findings is not clear; however, the effects may be the result of ketoacidosis secondary to metabolic disturbances. Because it is not yet clear if the 1:1 mixture of MCT:LCT, the mixture in Propofol-Lipuro 1%, infusions are associated with adverse developmental effects, this product should not be used in pregnant women unless there are no other FDA-approved products available and the clinical benefit clearly outweighs the risk. Otherwise, there are no concerns regarding the difference in the MCT/LCT formulation for Propofol-Lipuro 1% compared to the LCT-only formulation for Diprivan.

<u>Potential Benefits for the EUA of Propofol-Lipuro 1%</u>
The potential benefits of the EUA for Propofol-Lipuro 1% are as follows:

- Continued availability of propofol for ICU sedation for COVID-19 patients requiring mechanical ventilation is the primary benefit. While vaccine therapy is available, there is no cure for COVID-19 and the number of cases and deaths continue to rise.
- Increased availability of propofol for ICU sedation will potentially decrease the demand for other sedative agents, including dexmedetomidine and midazolam. Because these sedative medications are also used for, or are adjuncts to, procedural sedation and general anesthesia, any interruption in

supply may also impact availability in the operating room and non-operating room anesthetizing locations. Propofol-Lipuro 1% is likely to offset some of the demand throughout hospitals, not only in ICUs.

- Because the EUA is for 100 mL vials, the number of vial changes during patient infusion will be less than that required for 20 mL or 50 mL vial presentations. This will decrease the risk of medication error, due to less frequent infusion pump reprogramming, and the risk of microbial contamination, an important consideration for a formulation without a preservative agent.

Risks Associated with Administration of Propofol-Lipuro 1%

The risks associated with administration of Propofol-Lipuro 1% are as follows:

- The lack of an antimicrobial preservative agent can result in bacterial contamination in a drug product known to support microbial growth.
- Lipid overdose when propofol is administered in combination with total parental nutrition (TPN), solutions which contain varying amounts of lipid. Patients with critical illness are not able to tolerate oral feeding and commonly receive TPN in the ICU. Total lipid content calculations must always include the lipid content of the propofol administered for sedation. Of note, this is not a risk unique to Propofol-Lipuro 1%, but is possible with all formulations of propofol, including Diprivan.
- Based on embryofetal development MCT toxicity data in the published literature, there is a risk of development of neural tube defects in women of childbearing potential in the early stages of pregnancy. The expected human exposure to MCTs in Propofol-Lipuro 1% is within the equivalent range of doses administered in the study by Henwood *et al.* Based on existing data, it is not clear whether the MCT-containing lipid emulsions, such as Propofol-Lipuro 1%, are associated with more risk for neural tube defects as compared to the LCT-containing products. However, Propofol-Lipuro 1% is not recommended for use in pregnant patients unless there are no FDA-approved products available to maintain sedation for these patients during mechanical ventilation

Proposed Mitigation Strategies

The proposed mitigation strategies include the following:

- A label that clearly identifies the differences between Propofol-Lipuro 1% and FDA-approved propofol products.
- Limit Propofol-Lipuro 1% administration only to patients in the ICU setting for maintaining sedation.
- Limit the use of Propofol-Lipuro 1% to patients greater than 16 years old.
- Issuance of a Fact Sheet for healthcare providers with the following information:
    - A comparison table to identify the differences between Propofol-Lipuro 1% and the currently marketed Diprivan Injectable Emulsion 1%.

- Do not administer Propofol-Lipuro 1% 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.
- Required use of aseptic drug and infusion equipment handling, replacement of all infusion tubing and equipment every 12 hours, and replacement of each opened vial after 12 hours.

Conclusion

There is increased demand for availability of drugs to provide comfort and sedation to COVID-19 patients who are intubated and mechanically ventilated for prolonged periods of time in the ICU setting. The current supply of FDA-approved propofol products, including FDA-approved alternatives, is insufficient to fully meet the emergency need for the 100 mL presentation of the Propofol-Lipuro 1% product. There is previous clinical experience with MCT-containing propofol products in the U.S., both during previous shortages and currently during the COVID-19 pandemic. There is a long history of clinical use of Propofol-Lipuro 1% in Europe, beginning in Germany in 1999. This clinical experience contributes to the evaluation of whether the known and potential benefits of Propofol-Lipuro 1% outweigh the known and potential risks of the product in providing ICU sedation in critically ill COVID-19 patients. Specific risks identified that are associated with the Propofol-Lipuro 1% formulation can be mitigated, as discussed above.

Based on the scientific evidence available to FDA, it is reasonable to believe that Propofol-Lipuro 1% may be effective to maintain sedation via continuous infusion in patients greater than 16 years of age with suspected or confirmed COVID-19 who require mechanical ventilation in an ICU. Moreover, the overall benefit:risk profile and mitigation strategies support issuing an EUA for Propofol-Lipuro 1% Emulsion, to maintain sedation via continuous infusion in patients greater than 16 years of age with suspected or confirmed COVID-19 who require mechanical ventilation during the COVID-19 pandemic.

XXI. Considerations for Adverse Event (AE) Monitoring

The following conditions on adverse event reporting should be included in the letter authorization:

B. Braun Medical

B. Braun Medical 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 Medical 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.

Healthcare Facilities and Healthcare Providers

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.

XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

Refer to Letter of Authorization and the authorized Fact Sheets for Healthcare Providers.

XXIII. Information to Be Conveyed to Health Care Providers and Recipients of the Product

- Fact Sheet for Health Care Providers (See Section XXVI. Appendices)
- Fact Sheet for Patients and Parents/Caregivers (See Section XXVI. Appendices)

The authorized labeling (i.e., Fact Sheets) will initially be made available and disseminated electronically through B. Braun's website at: https://www.bbraunusa.com/en/company/newsroom/covid19.html#

For the first shipment of up to approximately (b) (4) units of 1% Propofol Lipuro, with each order confirmation or delivery notice, authorized distributors will notify the ordering hospital of the authorized labeling by either a) electronic communication that directs them to B. Braun's website containing the authorized labeling and/or electronically sending the

ordering hospital a PDF or other electronic version of the authorized labeling; or b) enclosure of paper copies of the authorized labeling in the shipment paperwork.

For the subsequent shipments (estimated shipping in May 2021), the 1% Propofol Lipuro carton pack of 10 units will contain a sticker/label with a QR code that will direct the customer to the authorized labeling available online.

FDA has considered B. Braun's proposal for the dissemination of the authorized labeling and finds it acceptable.

XXIV. Outstanding Issues/Data Gaps

There are no outstanding issues or data gaps.

XXV. References

Götzinger F, et al. COVID-19 in children and adolescents in Europe: a multinational, multicenter cohort study. *Lancet Child Adolesc Health* 2020; 4(9):653-661.

Henwood S, Wilson D, White R, Trimbo S. Developmental toxicity study in rats and rabbits administered an emulsion containing medium chain triglycerides as an alternative caloric source. *Fundam. Appl. Toxicol* 1997; 40:185-190.

Holshue M, et al. First case of 2019 novel Coronavirus in the United States*, N Engl J Med* 2020; 382:929-936.

Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020;323(13):1239-1242.

XXVI. Appendices

1. Fact Sheet for Health Care Providers
2. Fact Sheet for Patients and Parent/Caregivers

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALLISON MEYER
03/12/2021 10:31:49 AM

RENEE L PETIT-SCOTT
03/12/2021 10:37:56 AM

ALLA T BAZINI
03/12/2021 10:41:18 AM

RIGOBERTO A ROCA
03/12/2021 10:43:05 AM

WILLIAM H Dunn
03/12/2021 12:11:44 PM

US FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEUROSCIENCE
DIVISION OF ANESTHESIA, ADDICTION AND PAIN
ADDENDUM TO EUA SCIENTIFIC REVIEW

EUA:	0096
Product:	Propofol-Lipuro 1% Injectable Emulsion for Infusion
Applicant:	B.Braun Medical, Inc.
Intended Use:	To maintain sedation via continuous infusion in patients who require mechanical ventilation in an Intensive Care Unit (ICU) setting during Covid-19 pandemic
Intended Population:	Adult and pediatric patients (16 years of age and older)

This addendum summarizes the corrections made to the scientific review for EUA 96 issued on March 15, 2021. The corrections to the scientific review do not alter the efficacy and safety conclusion that resulted in issuance of EUA 96. The corrections to the scientific review do not alter the information in the approved EUA Healthcare Provider and Patient Fact Sheets.

The corrections are as follows:

1) Clarification of the Sponsor's name associated with both the NDA and the EUA, as B.Braun Medical, Inc. for NDA 207929 and B. Braun Melsungen AG as the Sponsor of the EUA.
2) Clarification that the manufacturing of the drug product in the EUA and the manufacturing of the Drug product in the NDA both take place at the same site.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JULIA C PINTO
04/09/2021 10:53:34 AM

WENDY I WILSON-LEE
04/09/2021 11:07:22 AM