HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CYPSEDO safely and effectively. See full prescribing information for CYPSEDO.

CYPSEDO™ (cipepofol injectable emulsion), for intravenous use [controlled substance scheduling pending]
Initial U.S. Approval: [pending controlled substance scheduling]

INDICATIONS AND USAGE

CYPSEDO is a general anesthetic drug indicated for induction of general anesthesia in adults undergoing surgery (1).

DOSAGE AND ADMINISTRATION

- Closely follow the preparation and administration instructions for CYPSEDO right before initiation of the surgery (2.1).
- The recommended weight-based CYPSEDO intravenous dose(s) and infusion duration depends on the patient's age group, BMI group, and by American Society of Anesthesiologists Physical Status (ASA-PS) classification. See Full Prescribing Information for the details (2.2).
- Administer an initial induction dose of CYPSEDO intravenously. If the induction is unsuccessful, an additional CYPSEDO dose may be administered intravenously over 10 seconds (approximately 1 minute after the end of the induction dose) (2.2).

DOSAGE FORMS AND STRENGTHS

Injectable emulsion: 50 mg/20 mL (2.5 mg/mL) single-dose vial (3).

CONTRAINDICATIONS

CYPSEDO is contraindicated in patients with (4, 5.1):

- Known hypersensitivity to CYPSEDO or any of its inactive ingredients.
- History of anaphylaxis to eggs, egg products, soybeans, or soy products.

WARNINGS AND PRECAUTIONS

- *Hypersensitivity Reactions Including Anaphylactic Reactions*: Life-threatening cases have been reported after CYPSEDO administration. Patients with a history of anaphylaxis to eggs, egg products, soybeans, or soy products may be at higher risk of anaphylaxis to CYPSEDO (5.1).
- *Risks of Microbial Contamination:* Always maintain strict aseptic technique during handling of CYPSEDO. Prior to CYPSEDO use, disinfect the rubber stopper of the vial with 70% isopropyl alcohol spray or an alcohol swab. Do not use a CYPSEDO vial in more than one person. Discard the opened/pierced or used vials within 12 hours (5.2).
- *Risks of Cardiac and Pulmonary Adverse Reactions:* During the use of CYPSEDO, continuously monitor patients for bradycardia, decreased blood pressure, respiratory depression, or decreased oxygen saturation. If these occur, measures should be taken to deal with them in a timely manner (5.3).
- *Risks of Neurotoxicity with Unapproved Use in Younger Pediatric Patients:* CYPSEDO is not approved for use in pediatric patients and not recommended for use in younger pediatric patients because of the risks of neurotoxicity observed in animal studies (5.4).

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥2%): hypotension, nausea, injection site pain, procedural pain, hypertension, procedural hypotension, asthenia, vomiting, dizziness, hypoxia, bradycardia, tachycardia, constipation, headache (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Haisco-USA Pharmaceuticals, Inc. at 1-866-358-7181 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Opioids and Other Sedatives: Concomitant use of CYPSEDO with opioids or other sedatives may result in more pronounced decreases in systolic and diastolic blood pressure and cardiac output (7).

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Use of CYPSEDO in pregnant patients should only be considered if the potential benefit to the mother and fetus outweighs its risks (8.1).
- *Patients with a BMI >40.kg/m²:* The recommended CYPSEDO dose in patients with BMI >40 kg/m² is lower than the recommended dose in patients with a BMI ≤40 kg/m² (8.8).
- *Patients with an ASA-PS III Classification:* The recommended CYPSEDO dose in patients with an ASA-PS III classification is lower than those with an ASA-PS I or II classification (8.9).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 5/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CYPSEDO is indicated for induction of general anesthesia in adults undergoing surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Important Preparation and Administration Instructions

CYPSEDO should be administered only by health care providers trained in the administration of induction of general anesthesia who are not involved in the conduct of the surgical procedure.

Prepare CYPSEDO just prior to initiation of the surgery in the following way *[see Warnings and Precautions (5.2)]*:

- Visually inspect CYPSEDO for particulate matter and discoloration (only use if the emulsion is uniform and the container is undamaged and unopened).
- Shake well before use.
- Disinfect the vial rubber stopper using 70% isopropyl alcohol or an alcohol swab.
- Withdraw CYPSEDO from the vial, using a sterile vent spike, into a sterile syringe immediately after the vial is opened or pierced.
- Label the syringe with the date and time the vial is opened/pierced.
- After the vial has been opened/pierced, immediately administer undiluted CYPSEDO intravenously.
- Do not use vials that have been opened/pierced for more than 12 hours.
- After use, flush the intravenous line to remove residual CYPSEDO.
- Discard any unused CYPSEDO, reservoirs, and/or dedicated administration tubing at the end of the surgery or at 12 hours, whichever occurs sooner.

Do not co-administer CYPSEDO with blood/serum/plasma because of the risk of aggregation. Administration of CYPSEDO with an in-line filter during anesthesia is **not** recommended.

2.2 Recommended Dose(s) and Administration

Table 1 includes the recommended weight-based CYPSEDO intravenous dose(s) by age group (adults less than 65 years of age or adults greater than or equal to 65 years of age), by body mass index (BMI) group (BMI less than or equal to 40 kg/m² or BMI greater than 40 kg/m²), and by American Society of Anesthesiologists Physical Status classification (ASA-PS) (I or II OR III). The recommended dosage of CYPSEDO for induction of general anesthesia in adults undergoing surgery with ASA-PS IV or higher has not been established.

Administer an initial induction dose of CYPSEDO intravenously. If the induction is unsuccessful with the initial induction dose, an additional CYPSEDO dose intravenously over 10 seconds (approximately 1 minute after the end of the induction dose) may be administered.

After induction of general anesthesia with CYPSDEO, use other drug(s) for maintenance of general anesthesia.

Table 1: Recommended CYPSEDO Intravenous Doses

Population	Initial Induction Dose	If Needed, Administer an Additional Bolus Over 10 Seconds (one minute after initial induction dose)
ASA-PS I or II		
Adults under 65 years of age with a BMI of 40 kg/m² or less	0.4 mg/kg over 30 seconds	0.2 mg/kg
Adults 65 years of age and older with a BMI of 40 kg/m² or less	0.3 mg/kg over 30 to 60 seconds	0.15 mg/kg
Adults of any age with a BMI greater than 40 kg/m²	0.2 mg/kg to 0.25 mg/kg over 30 seconds	50% of the initial induction dose
ASA-PS III		
Adults of any age with a BMI of 40 kg/m² or less	0.3 mg/kg over 30 to 60 seconds	0.15 mg/kg
Adults of any age with a BMI greater than 40 kg/m²	0.2 mg/kg to 0.25 mg/kg over 30 to 60 seconds	50% of the initial induction dose
ASA-PS IV or Higher		
The recommended dose of CYPSEDO for induction of general anesthesia in adults undergoing surgery with ASA-PS IV or higher has not been established.		

ASA-PS = American Society of Anesthesiologists – physical status; BMI = body mass index

3 DOSAGE FORMS AND STRENGTHS

Injectable emulsion: 50 mg/20 mL (2.5 mg/mL) white or off-white in single-dose vials.

4 CONTRAINDICATIONS

CYPSEDO is contraindicated in patients with a *[see Warnings and Precautions (5.1)]:*

- Known hypersensitivity to CYPSEDO or any of its inactive ingredients.
- History of anaphylaxis to eggs, egg products, soybeans, or soy products.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Anaphylactic Reactions

The use of CYPSEDO is contraindicated in patients with known hypersensitivity to CYPSEDO or any of its inactive ingredients and in patients with a history of anaphylaxis to eggs, egg products, soybeans, or soy products.

- Anaphylactic reactions, including life-threatening cases, have occurred after the use of CYPSEDO; clinical features of anaphylaxis, including hypotension, bronchospasm, and erythema can occur following CYPSEDO administration.
- Patients with a history of anaphylaxis to eggs, egg products, soybeans, or soy products may be at higher risk of anaphylaxis to CYPSEDO.

5.2 Risks of Microbial Contamination

Always maintain strict aseptic technique during handling of CYPSEDO. Prior to CYPSEDO use, disinfect the rubber stopper of the vial with 70% isopropyl alcohol spray or an alcohol swab.

Do not use a CYPSEDO vial in more than one person. Discard the opened/pierced or used vials and other reservoirs (such as syringes containing CYPSEDO) within 12 hours.

Although CYPSEDO contains edetate disodium to inhibit the growth rate of microorganisms for up to 12 hours, CYPSEDO can still support the growth of microorganisms because it is a preservative-free fat emulsion, which is conducive to microbial growth.

5.3 Risks of Cardiac and Pulmonary Adverse Reactions

During the use of CYPSEDO, continuously monitor patients for early signs of bradycardia, decreased blood pressure, respiratory depression, or decreased oxygen saturation, and intervene to correct cardiac and pulmonary adverse reactions in a timely manner if any of these occur.

Reports of bradycardia and cardiac arrest have occurred after CYPSEDO administration.

5.4 Risks of Neurotoxicity with Unapproved Use in Younger Pediatric Patients

The safety and effectiveness of CYPSEDO in pediatric patients for induction of general anesthesia have not been established, and CYPSEDO is not approved for use in pediatric patients.

Published animal studies demonstrated that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity increased neuronal apoptosis in the developing brain and resulted in long-term cognitive deficits when used for longer than three hours. The clinical significance of these findings is not clear. However, based on the available data, the window of vulnerability to these changes in young pediatric patients is believed to correlate with exposures of the anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans *[see Use in Specific Populations (8.4) and Nonclinical Toxicology (13.2)]*.

Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to such anesthetic drugs early in life and may result in adverse cognitive or behavioral effects. These studies have substantial limitations, and it is not clear if the observed effects are due to the anesthetic/sedation drug administration or other factors such as the surgery or underlying illness.

Anesthetic and sedation drugs are a necessary part of the care of children needing surgery, other procedures, or tests that cannot be delayed, and no specific medications have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

6 ADVERSE REACTIONS

The following serious or otherwise important adverse reactions are discussed elsewhere in the labeling:

- Anaphylactic reactions *[see Warnings and Precautions (5.1)]*
- Risks of microbial contamination *[see Warnings and Precautions (5.2)]*
- Risks of cardiac and pulmonary adverse reactions *[see Warnings and Precautions (5.3)]*
- Risks of neurotoxicity with unapproved use in younger pediatric patients *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of CYPSEDO for the induction of general anesthesia in adults undergoing surgery is supported by three double-blind, controlled clinical trials in adult patients undergoing general anesthesia (Trials 1, 2, and 3) *[see Clinical Studies (14)].* The trials included 1,080 patients aged 18 to 86 (723 patients treated with CYPSEDO and 357 patients treated with propofol injectable emulsion, referred to as propofol). Patients with a severe or uncontrolled cardiac, respiratory, neurological, or psychiatric disorder or undergoing emergency surgery were excluded from these clinical trials.

Table 2 summarizes the most common adverse reactions (≥2% of CYPSEDO-treated patients) that occurred in adult patients who underwent general anesthesia in Trials 1, 2, and 3.

Table 2: Most Common Adverse Reactions (≥2% of CYPSEDO-Treated Patients) That Occurred in Adults Who Underwent Induction of General Anesthesia in Trials 1, 2, and 3

Adverse Reactions	CYPSEDO (N=723) n (%)	Propofol Injectable Emulsion (N=357) n (%)
Hypotension	155 (21)	90 (25)
Nausea	155 (21)	70 (20)
Hypertension	88 (12)	38 (11)
Procedural pain	78 (11)	49 (14)
Procedural hypotension	61 (8)	41 (12)
Asthenia	52 (7)	37 (10)
Vomiting	40 (6)	22 (6)
Tachycardia	33 (5)	17 (5)
Hypoxia	24 (3)	13 (4)
Bradycardia	24 (3)	11 (3)
Dizziness	23 (3)	17 (5)

Adverse Reactions	CYPSEDO (N=723) n (%)	Propofol Injectable Emulsion (N=357) n (%)
Constipation	20 (3)	13 (4)
Injection site pain	19 (3)	56 (16)
Headache	17 (2)	10 (3)
Anemia	16 (2)	5 (1)

Perioperative Myoclonia

Perioperative myoclonia (e.g., myoclonus, involuntary muscle contractions, muscle twitching) occurred in CYPSEDO-treated patients.

Injection Site Pain

In Trials 1, 2, and 3, 17-19% of CYPSEDO-treated patients developed injection site pain, a significantly lower percentage compared to propofol-treated patients (see Table 3) *[see Clinical Studies (14)]*.

Table 3: Number and Proportion of Patients with Injection Site Pain on the Numeric Rating Scale ≥1 at the Time of Drug Administration in Adults Undergoing Surgery (Trials 1, 2, and 3)[1,2]

	CYPSEDO	Propofol Injectable Emulsion
Trial 1		
N	168	83
Number (Proportion) of Patients with NRS ≥1	30 (18%)	64 (77%)
Risk Difference (%)	-59%	
95% CI (%)	(-70%, -48%)	
P-value[3]	<0.0001	
Trial 2		
N	255	128
Number (Proportion) of Patients with NRS ≥1	42 (17%)	58 (45%)
Risk Difference (%)	-28%	
95% CI (%)	(-38%, -19%)	
P-value[3]	<0.001	
Trial 3		
N	300	145
Number (Proportion) of Patients with NRS ≥1	56 (19%)	86 (59%)
Risk Difference (%)	-41%	
95% CI (%)	(-50%, -32%)	
P-value[3]	<0.001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; NRS = numeric rating scale

[1] Full analysis set
[2] Prior to receiving CYPSEDO, four patients across Trials 1, 2, and 3 received lidocaine (including 3 patients who received intravenous lidocaine and 1 patient who received lidocaine by an undetermined route of administration). Prior to receiving propofol, no patients received intravenous lidocaine in Trials 1, 2, or 3.
[3] The p-value for between group differences was calculated using the CMH test and the stratification factors American Society of Anesthesiologists physical status (I-II and III), age (<65 and ≥65 years), and body mass index (<35 and ≥35 kg/m²) in the trial randomization.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of CYPSEDO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Anaphylactic shock *[see Warnings and Precautions (5.1)]*.
- Phlebitis

7 DRUG INTERACTIONS

Opioids and Other Sedatives

The concomitant use of CYPSEDO and opioids or other sedatives (e.g., benzodiazepines, barbiturates, chloral hydrate, droperidol) may result in more pronounced decreases in systolic and diastolic blood pressure and cardiac output.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The use of CYPSEDO in pregnant patients should only be considered if the potential benefit to the mother and fetus outweighs its risks. Pregnant patients should be informed of possible hazards to the mother and fetus.

In an animal reproductive study, increased resorptions, increased pre- and post-implantation loss, decreased live fetuses, and decreased uterus weights, were observed with intravenous administration of cipepofol to rats prior to mating through early gestation at clinically relevant exposures. The pharmacological effect (anesthesia) of cipepofol on the maternal rats is probably responsible for these adverse effects.

Published studies in pregnant primates demonstrated that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity (for longer than three hours) during the period of peak brain development increased neuronal apoptosis in the developing brain of the primate offspring. There are no data on exposures in pregnant primates corresponding to periods prior to the third trimester in humans. The clinical significance of these nonclinical findings is not known, and the benefits of appropriate general anesthesia in pregnant patients who require general anesthesia should be balanced with the potential risks suggested by the nonclinical data.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other

adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data: In the fertility and early embryonic development toxicity study, female rats were administered daily intravenous injections of cipepofol 2 weeks before mating to Gestation Day 6 at doses of 1.2, 2.5, and 5 mg/kg (0.2, 0.5, and 1.3 times the human induction dose (HID) of 0.6 mg/kg based on area under the curve [AUC]). Increased resorptions and post-implantation loss along with decreased live fetuses and gravid uterus weights were observed at 0.5 times the HID based on AUC while an increase in pre-implantation loss was observed at 1.3 times the HID based on AUC.

In embryo-fetal developmental toxicity studies, pregnant rats were administered daily intravenous injections of cipepofol at doses of 1.2, 2.5, and 5 mg/kg (0.3, 0.8, and 1.7 times the HID of 0.6 mg/kg based on AUC), and female rabbits were administered daily intravenous injections of cipepofol at doses of 0.75, 1.5, and 3 mg/kg (0.02, 0.06, and 0.2 times the HID based on AUC) during the period of organogenesis. Mortalities were observed in maternal high dose animals due to the pharmacological anesthetic effect but cipepofol did not cause any fetal malformations in rats or rabbits.

In the pre- and postnatal development toxicity study, pregnant rats administered daily intravenous injections of cipepofol at doses of 1.2, 2.5, and 5 mg/kg (0.3, 0.8, and 1.7 times the HID based on AUC) from Gestation Day 6 to Lactation Day 21 resulted in no adverse developmental effects nor behavioral alterations (i.e., learning and memory as tested in a Morris water maze) in the offspring. Mortality was observed in a high dose female (1.7 times the HID based on AUC) due to the pharmacological anesthetic action of cipepofol.

In a published study in primates, administration of an anesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the fetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits *[see Warnings and Precautions (5.4), Use in Specific Populations (8.4), and Nonclinical Toxicology (13.2)]*.

8.2 Lactation

Risk Summary

There are no data on the presence of cipepofol in human milk, the effects on a breastfed infant, or the effects on milk production. Cipepofol is present in animal milk *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CYPSEDO and any potential adverse effects on the breastfed child from CYPSEDO or from the underlying maternal condition.

Data
Daily intravenous injections of cipepofol to female rats at doses up to 5 mg/kg (1.7 times the HID of 0.6 mg/kg based on AUC) from Gestation Day 6 to Lactation Day 21 resulted in cipepofol exposure in milk up to 40 times the plasma levels in lactating females 30 minutes to 1 hour after administration, while it was not detected in nursing rat pups.

8.4 Pediatric Use

The safety and effectiveness of CYPSEDO have not been established in pediatric patients and CYPSEDO use is not recommended for use in younger pediatric patients because of the risks of neurotoxicity *[see Warnings and Precautions (5.4) and Nonclinical Toxicology (13.2)]*.

Risks of Unapproved Use of CYPSEDO in Younger Pediatric Patients
Published juvenile animal studies demonstrate that the administration of anesthetic and sedation drugs, such as CYPSEDO, that either block NMDA receptors or potentiate the activity of GABA during the period of rapid brain growth or synaptogenesis, results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparison across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of ketamine that produced a light surgical plane of anesthesia did not increase neuronal cell loss; however, treatment of 5 hours or longer of isoflurane increased neuronal cell loss. Data from isoflurane-treated rodents and ketamine-treated primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

8.5 Geriatric Use

In Trials 1, 2, and 3, 22% (241/1080) of the adult patients were 65 years of age or older, including 22% (161/723) of CYPSEDO-treated patients. In these trials, 5% (57/1,080) of the adult patients were 75 years of age or older, including 5% (37/723) of CYPSEDO-treated patients. In all three trials, the CYPSEDO dose for patients 65 years or older was an initial dose of 0.3 mg/kg and an additional dose of 0.15 mg/kg if needed. The duration over which the initial dose was administered in Trial 1 was 30 seconds but in Trials 2 and 3 was 30 to 60 seconds *[see Dosage and Administration (2.2)]*.

Safety Evaluation in Geriatric Patients
No overall differences in safety of CYPSEDO were observed between patients 65 years of age and older and adult patients less than 65 years of age.

Efficacy Evaluation in Geriatric Patients

- In Trials 1, 2, and 3, patients 65 years of age and older (who received an initial CYPSEDO dose of 0.3 mg/kg and a possible second dose of 0.15 mg/kg) had numerically similar rates of successful induction of anesthesia as adult patients less than 65 years of age (who received a larger initial CYPSEDO dose of 0.4 mg/kg with a possible second dose of 0.2 mg/kg).

- In the CYPSEDO group, in:
  - Trial 1 (intravenous fentanyl administration prior to CYPSEDO administration), 26% (7/27) of adult patients 65 years of age or older required the additional CYPSEDO dose or rescue for successful induction of anesthesia, compared to 21% (29/141) of adult patients less than 65 years of age.
  - Pooled Trials 2 and 3 (intravenous midazolam and fentanyl administration prior to CYPSEDO administration), 4% (6/134) of adult patients 65 years of age or older required the additional CYPSEDO dose or rescue for successful induction of anesthesia, compared to 5% (21/421) of adult patients less than 65 years of age.

Pharmacokinetics and Pharmacodynamics in Geriatric Patients

No clinically meaningful differences in the pharmacokinetics of cipepofol were observed in patients 65 years of age or older (n=8) who received an induction dose of 0.4 mg/kg compared to adult patients less than 65 years of age (n=8) who received an induction dose of 0.4 mg/kg in a Phase 1 clinical study.

Patients 65 years of age or older who received a CYPSEDO dose of 0.3 mg/kg had similar pharmacodynamics (Modified Observer's Assessment for Alertness and Sedation scale (MOAA/S) and bispectral index (BIS)) results compared with adult patients less than 65 years of age who received a dose of 0.4 mg/kg *[see Clinical Pharmacology (12.2, 12.3)]*.

8.6 Renal Impairment

There are no clinical study data regarding the use of CYPSEDO in patients with severe renal impairment (RI). Use of CYPSEDO in patients with severe RI is not recommended.

There were no clinically significant differences in the pharmacokinetics or pharmacodynamics (MOAA/SBIS) of cipepofol in adult patients with chronic mild to moderate RI compared to adults without RI. The recommended dose of CYPSEDO in patients with mild to moderate RI is the same as that for patients without RI.

The effects of acute renal failure on the pharmacokinetics of cipepofol have not been studied.

8.7 Hepatic Impairment

There are no clinical study data regarding the use of CYPSEDO in patients with severe hepatic impairment (HI). Use of CYPSEDO in patients with severe HI is not recommended.

There were no clinically significant differences in pharmacokinetics or pharmacodynamics (MOAA/S and BIS) of cipepofol in patients with chronic mild to moderate HI compared to adults without HI. The recommended dose of CYPSEDO in patients with mild to moderate HI is the same as that for patients without HI.

8.8 Patients with BMI >40 kg/m²

The recommended CYPSEDO dose in adult patients with BMI >40 kg/m² is lower than the recommended dose in adult patients with a BMI ≤40 kg/m² [*see Dosage and Administration (2.2)]*.

In a population pharmacokinetic analysis, compared to those with a BMI ≤40 kg/m², there was increased cipepofol exposure in patients with a BMI >40 kg/m² which may increase the risk of CYPSEDO-associated adverse reactions.

Safety Evaluation by BMI Status
In Trials 1, 2, and 3, with the use of lower dose(s) in adult patients with a BMI >40 kg/m², the safety profile of CYPSEDO was similar to adult patients with BMI ≤40 kg/m² who received a higher dose(s).

Efficacy Evaluation by BMI Status
- In Trials 1, 2, and 3, adult patients with BMI >40 kg/m² (who received an initial CYPSEDO dose of 0.2 mg/kg to 0.25 mg/kg with a possible second dose 50% of the initial dose) had numerically similar rates of successful induction of anesthesia as adult patients with a BMI ≤40 kg/m² (who received a larger initial CYPSEDO dose of 0.4 mg/kg with a possible second dose of 0.2 mg/kg).
- In the CYPSEDO group in:
  - Trial 1 (intravenous fentanyl administration prior to CYPSEDO administration), 50% (6/12) of adult patients BMI >40 kg/m² required the additional CYPSEDO dose or rescue for successful induction of anesthesia, compared to 19% (30/156) of adult patients BMI ≤40 kg/m².
  - Pooled Trials 2 and 3 (intravenous midazolam and fentanyl administration prior to CYPSEDO administration), 27% (13/49) of adult patients BMI >40 kg/m² required the additional CYPSEDO dose or rescue for successful induction of anesthesia, compared to 3% (14/506) of adult patients BMI ≤40 kg/m².

8.9 Patients with ASA-PS Classification III or Higher
In Trials 1, 2, and 3, 19% (203/1,080) of adult patients with ASA-PS III, including 19% (140/723) of adult patients treated with CYPSEDO, were enrolled *[see Clinical Studies (14)]*. Of the CYPSEDO-treated patients with ASA-PS III, 69% (97/140) had a BMI ≤40 kg/m². The recommended CYPSEDO dose and rate of administration in patients with ASA-PS III are lower than for those with ASA-PS I or II *[see Dosage and Administration (2.2)]*.

Safety Evaluation by ASA-PS Classification (ASA-PS III vs. ASA-PS I or II)
In Trials 1, 2, and 3, a lower CYPSEDO dose was used for patients with ASA-PS III compared to those with an ASA-PS I or II. In Trials 2 and 3 the duration of CYPSEDO injection was 30-60 seconds for patients with ASA-PS III compared to 30 seconds for patients with ASA-PS I or II. In Trials 1, 2, and 3, the safety profile of a lower CYPSEDO dose in patients with ASA-PS III was similar to that of patients with ASA-PS I or II with a higher dose.

Efficacy Evaluation by ASA-PS Classification (ASA-PS III vs. ASA-PS I or II)
- In Trials 1, 2, and 3, adult patients with ASA-PS III (who received an initial CYPSEDO dose of 0.3 mg/kg with a possible second dose of 0.15 mg/kg) had numerically similar rates of successful induction of anesthesia as adult patients with ASA-PS I or II (who received a larger initial CYPSEDO dose of 0.4 mg/kg with a possible second dose of 0.2 mg/kg)

- In the CYPSEDO group in:
  - Trial 1 (intravenous fentanyl administration prior to CYPSEDO administration), 25% (3/12) of adult patients with ASA-PS III required the additional CYPSEDO dose or rescue for successful induction of anesthesia, compared to 21% (33/156) of adult patients with ASA-PS I or II.
  - Pooled Trials 2 and 3 (intravenous midazolam and fentanyl administration prior to CYPSEDO administration), 11% (14/128) of adult patients with ASA III required the additional CYPSEDO dose or rescue for successful induction of anesthesia, compared to 3% (13/427) of adult patients with ASA-PS I or II.

Patients with ASA-PS Classification IV or Higher

No adult patients with ASA-PS IV or higher were enrolled. The safety of the use of CYPSEDO in anesthesia induction in adult patients with ASA-PS IV or higher has not been evaluated. The recommended dosage of CYPSEDO for induction of general anesthesia in adults undergoing surgery with ASA-PS IV or higher has not been established.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

CYPSEDO contains cipepofol. (Controlled substance schedule to be determined after review by the Drug Enforcement Administration).

9.2 Abuse

CYPSEDO is a central nervous system (CNS) depressant and has a potential for abuse. Abuse of CYPSEDO may lead to substance use disorder, including addiction. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

CYPSEDO can also be misused. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Misuse, like abuse, is often associated with higher doses and/or more frequent use of the drug, which may lead to adverse reactions similar to those seen in the context of abuse and substance use disorder.

In a human abuse potential crossover study conducted in individuals with a history of recreational CNS depressant use, subjective effects of single intravenous bolus injections of CYPSEDO 0.175 mg/kg and 0.2 mg/kg were compared to subjective effects of single intravenous bolus injections of propofol 0.725 mg/kg and placebo.

- On the primary outcome measure of “drug liking,” there were no statistically significant differences between CYPSEDO 0.175 mg/kg and 0.2 mg/kg doses and propofol.
- CYPSEDO 0.175 mg/kg and 0.2 mg/kg doses produced mean responses similar to propofol on the secondary measures of “take drug again,” “overall drug liking,” and “drug high.”

- Mean drowsiness/alertness scores were similar for CYPSEDO 0.175 mg/kg and 0.2 mg/kg doses and propofol and were lowest (increased drowsiness) for both CYPSEDO doses and propofol at the first measured timepoint, which was 15 minutes post-dose.

There are reports of abuse of other intravenous emulsion general anesthetics for recreational and other nonmedical purposes, which have resulted in fatalities and other injuries. Instances of self-administration of intravenous emulsion general anesthetics by health care providers have also been reported, which have resulted in fatalities and other injuries. To mitigate these risks, store and manage inventories of CYPSEDO, including restriction of access and accounting procedures as appropriate to the clinical setting.

9.3 Dependence

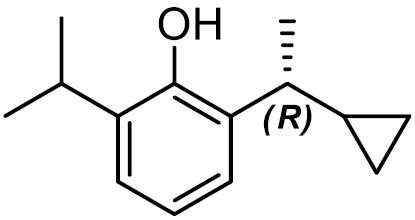
Although CYPSEDO was not systematically evaluated for physical dependence during clinical development and is likely not a risk relevant to induction of general anesthesia in adults undergoing surgery (its approved use), there are reports of withdrawal symptoms associated with discontinuation of other intravenous emulsion general anesthetics following prolonged use. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

10 OVERDOSAGE

Overdose of CYPSEDO may cause cardiovascular and respiratory depression. Respiratory depression can be treated with mechanical ventilation, while cardiovascular depression may require other measures to increase cardiac output, (e.g., administering volume expansion, vasopressor drugs).

11 DESCRIPTION

CYPSEDO (cipepofol injectable emulsion) is an anesthetic available as a sterile, white or off-white emulsion for intravenous administration. The active ingredient, cipepofol, is chemically described as 2-[(1R)-1-cyclopropylethyl]-6-isopropyl-phenol. Its structural formula is:



Molecular Formula: $C_{14}H_{20}O$
Molecular Weight: 204.31 grams/mol

Cipepofol is practically insoluble in water. The log octanol/water partition coefficient is 4.36.

Each mL of CYPSEDO (cipepofol injectable emulsion) contains cipepofol 2.5 mg and the following inactive ingredients: edetate disodium anhydrous 0.05 mg (equivalent to edetate disodium 0.055 mg), egg phospholipids 12 mg, glycerin 22.5 mg, medium-chain triglycerides

50 mg, sodium oleate 0.3 mg, soybean oil 50 mg, and water for injection, with sodium hydroxide to adjust pH. CYPSEDO is isotonic and has a pH of 6.0 to 9.0. Egg phospholipids are derived from eggs, and soybean oil is derived from soybeans.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of CYPSEDO for induction of general anesthesia in adults undergoing surgery is poorly understood. However, cipepofol is thought to produce anesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through ligand-gated $GABA_A$ receptors.

12.2 Pharmacodynamics

The anesthetic effects of CYPSEDO were assessed using the MOAA/S and BIS in a randomized, dose-escalation, open-label, two-way crossover clinical pharmacology trial that evaluated the pharmacodynamics and pharmacokinetics of cipepofol compared with propofol at different doses in healthy male subjects. An MOAA/S score of 0 indicates that the patient is unresponsive and score 5 indicates that the patient is fully alert; a BIS score of 0 indicates that there is no detectable brain activity, and a score of 100 indicates that the patient is fully conscious and alert. A total of 19 subjects were enrolled in the trial and were randomized to 1 of 3 treatment sequences. For the 0.4 mg/kg CYPSEDO dose (administered over 1 minute) in 6 subjects, the:

- MOAA/S score decreased after CYPSEDO administration, and all subjects reached a MOAA/S ≤1 within 2 minutes after dosing. The mean (standard deviation [SD]) time to complete alertness after dosing was 13.3 (6.2) minutes after dosing.
- The BIS decreased to the minimum after CYPSEDO administration with a mean (SD) BIS nadir of 42.5 (5.5) at median time of 2.3 minutes.

MOAA/S and BIS parameters in geriatric patients, patients with HI, and patients with RI were comparable to healthy adults *[see Clinical Pharmacology (12.3)]*.

Cardiac Electrophysiology

At the recommended initial CYPSEDO dose for patients with ASA-PS I or II, <65 years old, and BMI ≤40 kg/m² of 0.4 mg/kg intravenously over 30 seconds, clinically significant QTc interval prolongation was not observed.

12.3 Pharmacokinetics

Pharmacokinetic parameters were evaluated in 48 healthy adult patients, who received a single intravenous bolus of CYPSEDO 0.4 mg/kg administered over 30 seconds. The mean (SD) venous maximum plasma concentration (C_{max}) of cipepofol (administered over 30 seconds) was 2,790 (1,890) ng/mL and mean (SD) area under the plasma concentration time curve from 0 to infinity ($AUC_{0\text{-}inf}$) was 256 (54.9) ng.h/mL. In dose ranging studies, pharmacokinetics were linear and dose proportional over the dose range of 0.128 to 0.81 mg/kg.

Distribution

Cipepofol has a large volume of distribution of 4.19±1.10 L/kg. Cipepofol is highly protein bound (approximately 99%) and protein binding was unaffected by mild or moderate RI or HI.

Elimination

After a single intravenous bolus of CYPSEDO 0.4 mg/kg, the mean (SD) clearance was 1.63 (0.357) L/h/kg, and the mean (SD) half-life was 1.81 (0.431) hours.

Metabolism: Cipepofol is extensively metabolized by UGT enzymes (predominantly UGT1A9) and CYP2B6, and to a minor extent, CYP1A2 and CYP2C19.

Following a single intravenous dose of 0.8 μCi/0.4 mg/kg [^{14}C]-cipepofol (radiolabeled cipepofol), cipepofol represented approximately 1.1% of total plasma radioactivity, with the major metabolite M4, a pharmacologically inactive O-glucuronide metabolite, accounting for 71% of total plasma radioactivity.

Excretion: While cipepofol is not excreted in the urine, renal excretion is the primary route of elimination for the metabolites. In a mass balance study, approximately 85% of the administered cipepofol dose was excreted in urine, with glucuronide metabolites M4 and M5-1 accounting for 51.6% and 19.3% of the administered dose, respectively.

Specific Populations

Population pharmacokinetics analysis indicated that weight, sex, race, and age were covariates on CYPSEDO clearance or volume. Neither sex nor race had a clinically meaningful impact on cipepofol exposure.

Geriatric Patients: Cipepofol exposures following intravenous administration of a CYPSEDO 0.4 mg/kg dose were similar in adults 65 years of age and older and those less than 65 years of age, indicating that age did not have a significant effect on plasma cipepofol exposure. With regard to PD effects, adult patients 65 years of age or older who received a CYPSEDO dose of 0.3 mg/kg had similar pharmacodynamic (MOAA/S and BIS) results compared with adult patients less than 65 years of age who received a dose of 0.4 mg/kg *[see Dosage and Administration (2.2) and Use in Specific Populations (8.5)]*.

Patients with Renal Impairment: In a clinical pharmacology study of CYPSEDO in patients with chronic mild and moderate RI and patients without RI, mean C_{max} was slightly decreased in those with worse renal function, but $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values showed no clear trend with worse renal function:

- Mild RI (i.e., estimated GFR [eGFR]: 60 to 89 mL/minute/1.73 m²): geometric mean AUC values were increased by approximately 12% to 13%, and C_{max} was decreased by approximately 32% compared with those without RI.
- Moderate RI (i.e., eGFR: 30 to 59 mL/minute/1.73 m²): geometric mean AUC values were similar, and C_{max} was decreased by approximately 19% compared with those without RI.
- Severe RI (i.e., eGFR: less than 30 mL/minute/1.73 m² with or without dialysis): pharmacokinetics was not assessed and is not known.

MOAA/S and BIS parameters were similar across patients with mild RI, moderate RI, and without RI groups *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment: In a clinical pharmacology study, mean cipepofol C_{max} showed no clear trend when comparing patients with normal hepatic function and patients with mild HI (Child-Pugh A) or moderate HI (Child-Pugh B), while $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ increased slightly with worse HI:

- Mild HI: geometric mean AUC values were increased by approximately 10% to 12%, and C_{max} was increased by 14% compared with those without HI.
- Moderate HI: geometric mean AUC values were increased by approximately 22% to 30% while C_{max} was not changed compared with those without HI.
- Severe HI: pharmacokinetics was not assessed and is not known.

Sedation assessed by MOAA/S and BIS nadir showed similar trends in patients with mild HI, moderate HI, and without HI, indicating that there were no effects of mild and moderate HI on sedation *[see Use in Specific Populations (8.7)]*.

Patients with BMI >40 kg/m²: In population pharmacokinetics analyses, there was increased cipepofol exposure with increasing lean body weight. Specifically, simulated CYPSEDO doses of 0.2 mg/kg to 0.25 mg/kg in patients with BMI >40 kg/m² were predicted to have similar exposure to a dose of 0.4 mg/kg in patients with BMI ≤40 kg/m²; therefore, in Trials 1, 2, and 3 *[see Clinical Studies (14)],* patients with BMI >40 kg/m² received a lower CYPSEDO dose than those with a BMI ≤40 kg/m² [*see Dosage and Administration (2.2) and Use in Specific Populations (8.8)]*.

Drug Interaction Studies

Clinical Studies: There was no significant pharmacokinetic/pharmacodynamic drug interaction of cipepofol with rifampicin (CYP2B6 inducer, UGT1A9 inducer), voriconazole (CYP2B6 inhibitor), mefenamic acid (UGT1A9 inhibitor), or divalproex.

In Vitro Studies

- *Metabolizing enzymes:* Cipepofol inhibited CYP2B6 and CYP2C19 in vitro, while its major metabolite, M4, did not inhibit any CYP enzymes. Cipepofol also inhibited UGT1A9 metabolism in vitro. Based on the rapid decline in cipepofol concentrations following administration of a 0.4 mg/kg CYPSEDO dose, there are not anticipated to be any clinically relevant drug interactions affecting CYP2B6, CYP2C19, and UGT1A9 substrates.

  Cipepofol and its major metabolite, M4, did not induce CYP1A2, CYP2B6, and CYP3A4 at clinically relevant concentrations.

- *Drug transporters:* Cipepofol and M4 are not substrates of P-gp, BCRP, OAT1, OCT2, MATE1, and MATE2K. Cipepofol was not a substrate of OAT3, OATP1BI, and OATP1B3, while M4 was possibly a substrate of these transporters. Cipepofol was not an inhibitor of P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2K. M4 was not an inhibitor of P-gp, BCRP, OCT2 and MATE2K, but at high concentrations showed

inhibitory activity for OAT1, OAT3, OATP1B1, OATP1B3, and MATE1. Based on in vitro studies, cipepofol and M4 are not expected to show clinically relevant inhibition of any drug transporters.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of cipepofol has not been evaluated.

Mutagenesis

Cipepofol was not mutagenic in the in vitro bacterial reverse mutation assay (Ames test). Cipepofol was non-clastogenic in the chromosome aberration study. In the in vivo mouse micronucleus study, cipepofol was non-genotoxic as it did not induce micronuclei formation in polychromatic erythrocytes in bone marrow.

Impairment of Fertility

Fertility in male or female rats was not affected after daily intravenous injections of cipepofol at doses up to 5 mg/kg (1.3 times the HID based on AUC) administered from 4 weeks prior to mating initiation until completion in males and 2 weeks prior to mating to Gestation Day 6 in females.

13.2 Animal Toxicology and/or Pharmacology

There was no evidence of local vascular irritation following single intravenous or repeated daily (7 days) intra-arterial dosing of cipepofol to rabbits. Minimal local irritation was observed in rabbits following repeated daily (7 days) subcutaneous dosing of cipepofol.

Effects on the Use of Anesthetic Drugs in Animals

Published studies in animals demonstrate that the use of anesthetic drugs during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life but may extend out to approximately 3 years of age in humans. In primates, exposure to 3 hours of an anesthetic regimen that produced a light surgical plane of anesthesia did not increase neuronal cell loss; however, anesthetic treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with subtle but prolonged cognitive deficits in learning and memory *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1, 8.4)]*.

14 CLINICAL STUDIES

Efficacy of CYPSEDO for induction of general anesthesia in adults undergoing surgery was assessed in three randomized, double-blind, propofol-controlled multicenter Phase 3 trials (Trials 1, 2, and 3). These trials assessed efficacy in 1,079 adult patients aged 18 to 86 who underwent elective surgeries. Patients undergoing cardiac, neurosurgical, or emergency surgeries were not enrolled in these trials.

Dosages of CYPSEDO and propofol in these trials varied by age, BMI, and ASA-PS classification and included an initial dose plus a possible additional dose that was administered one minute later over 10 seconds, if needed, to achieve MOAA/S ≤1.

- CYPSEDO Dose(s): For adults with BMI ≤40 kg/m², total body weight was used to determine the CYPSEDO dose; for adults with BMI >40 kg/m², lean body weight was used to determine the CYPSEDO dose.
  - For adults <65 years of age, ASA-PS I or II, and BMI ≤40 kg/m²: CYPSEDO 0.4 mg/kg by slow intravenous injection over 30 ±5 seconds, and if needed, an additional 0.2 mg/kg intravenous dose.
  - For ≥65 years of age, ASA-PS I or II, and BMI ≤40 kg/m²: CYPSEDO 0.3 mg/kg by slow intravenous injection over 30 seconds (Trial 1) or CYPSEDO 0.2 to 0.3 mg/kg over 30 to 60 seconds (Trials 2 and 3), and if needed, an additional intravenous dose that was 50% of the initial dose.
  - For adults of any age, ASA-PS III, and BMI ≤40 kg/m², CYPSEDO 0.4 mg/kg by slow intravenous injection over 30 seconds (Trial 1) or CYPSEDO 0.2 to 0.3 mg/kg over 30 to 60 seconds (Trials 2 and 3), and if needed, an additional intravenous dose that was 50% of the initial dose.
  - For adults of any age, any ASA-PS classification, and BMI >40 kg/m²: CYPSEDO 0.4 mg/kg based on lean body weight by slow intravenous injection over 30 seconds, and if needed, an additional intravenous dose that was 50% of the initial dose.
- Propofol Injectable Emulsion Dose(s): Propofol injectable emulsion (referred to as propofol) 2 mg/kg by slow intravenous injection over 30 ±5 seconds, and if needed, followed by an additional 1 mg/kg dose by slow intravenous injection over 30 seconds administered one minute later. The propofol doses were reduced by 25% to 50% in adult patients with a BMI >40 kg/m^2 or age 65 or older in Trials 1, 2, and 3. In Trials 2 and 3, propofol doses were also reduced by 25% to 50% in patients classified as ASA-PS III.

Premedication

The premedication regimens differed across the trials:

- In Trial 1, patients received intravenous fentanyl 1 mcg/kg prior to study drug administration.
- In Trials 2 and 3, patients first received intravenous midazolam 0.04 mg/kg (up to maximum of 3 mg) 5 minutes (±30 seconds) prior to study drug administration, followed by intravenous fentanyl 1 mcg/kg, then study drug administration.

Efficacy Endpoints

Efficacy in all three trials was assessed based on the success rate of general anesthesia induction. Successful general anesthesia induction occurred when both of the following conditions were met:

1. Induction success (MOAA/S ≤1) after administration of the study drug, and
2. One or no additional dose required without use of a rescue drug for induction of anesthesia.

Comparative safety was assessed in these trials based on the proportion of patients with any injection site pain at time of drug administration on the numeric rating scale (NRS) ≥1 *[see Adverse Reactions (6.1)]*.

Baseline Demographic and Important Disease Characteristics

Among the patients evaluated in Trials 1, 2, and 3, 61% were female, 80% were White, 16% were Black or African American, and 1% were Asian; 23% identified as Hispanic or Latino. In the three trials, 81% of the patients were ASA-PS I or II and 19% were ASA-PS III, and no patients were ASA-PS IV or higher. In the three trials, 92% had a BMI ≤40 kg/m².

Efficacy Results

In Trials 1, 2, and 3, the lower bound of the 95% confidence interval of the difference in success rate of anesthesia induction between CYPSEDO and propofol in adults undergoing surgery exceeded -8% (see Table 4). In these trials, CYPSEDO was shown to be noninferior to propofol in the induction of general anesthesia in adults undergoing surgery.

Table 4: Success Rate of Anesthesia Induction in Adults Undergoing Surgery (Trials 1, 2, and 3)[1]

	CYPSEDO	Propofol Injectable Emulsion
Trial 1[2][3]		
N	168	83
Successful Anesthesia Induction, n (%)	163 (97.0%)	81 (97.6%)
Risk Difference (%)[5]	-0.57	
95% CI (%)[5]	(-5.4, 4.2)	
Trial 2[2][4]		
N	255	128
Successful Anesthesia Induction, n (%)	253 (99.2)	128 (100.0)
Risk Difference (%)[5]	-0.78	
95% CI (%)[5]	(-4.11, 2.55)	
Trial 3[2][4]		
N	300	145
Successful Anesthesia Induction, n (%)	298 (99.3%)	143 (98.6%)
Risk Difference (%)[5]	0.71	
95% CI (%)[5]	(-2.62, 4.04)	

CI = confidence interval
[1] Full Analysis Set.
[2] The non-inferiority margin was -8%.
[3] In Trial 1, patients received intravenous fentanyl 1 mcg/kg prior to study drug administration.
[4] In Trials 2 and 3, patients first received intravenous midazolam 0.04 mg/kg (up to maximum of 3 mg) 5 minutes (±30 seconds) prior to study drug administration, followed by intravenous fentanyl 1 mcg/kg, then study drug administration.
[5] Risk difference (CYPSEDO - Propofol Injectable Emulsion) and 95% CI were estimated by Farrington-Manning method.

The percentage of adult patients with a MOAA/S ≤1 who received the initial dose of study drug but did not require an additional dose of study drug or a rescue drug was:

- 79% (132/168) for those in the CYPSEDO group and 83% (69/83) for those in the propofol group in Trial 1 (intravenous fentanyl administration prior to CYPSEDO administration).
- 95% (528/555) for those in the CYPSEDO group and 99% (269/273) for those in the propofol group in pooled Trials 2 and 3 (intravenous midazolam and fentanyl administration prior to CYPSEDO administration).

Injection Site Pain Results
CYPSEDO-treated patients had a statistically significant lower frequency of injection site pain than propofol-treated patients *[see Adverse Reactions (6.1)]*.

Prior to CYPSEDO administration, four adult patients across Trials 1, 2, and 3 received lidocaine (including 3 patients who received intravenous lidocaine and 1 patient who received lidocaine by an undetermined route of administration) and none reported injection site pain, and no adult patient in Trials 1, 2, and 3 received intravenous lidocaine prior to propofol administration. Excluding patients pre-treated with intravenous lidocaine from the secondary endpoint analysis did not affect the finding of lower frequency of injection site pain in CYPSEDO-treated patients compared to propofol-treated patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

CYPSEDO (cipepofol injectable emulsion) is available as a sterile, white or off-white emulsion as follows:

Strength	
50 mg/20 mL (2.5 mg/mL)	20 mL ready-to-use single-dose vial for intravenous administration; 5, 10, or 25 vials per package

Store CYPSEDO vials at 2ºC to 25ºC (35.6ºF to 77ºF). Do not freeze. Shake well before use.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions Including Anaphylactic Reactions
Inform patients that anaphylactic reactions, including life-threatening cases, have occurred after the use of CYPSEDO *[see Warnings and Precautions (5.1)]*.

Risks of Cardiac and Pulmonary Adverse Reactions
Inform patients that bradycardia and cardiac arrest have occurred after CYPSEDO administration *[see Warnings and Precautions (5.3)]*.

Effect of Anesthetic and Sedation Drugs on Early Brain Development
Studies conducted in young animals and children suggest repeated or prolonged use of general anesthetic and sedation drugs in children younger than 3 years may have negative effects on their developing brains *[see Warnings and Precautions (5.4)]*. Discuss with parents and caregivers the benefits, risks, and timing and duration of surgery or procedures requiring anesthetic and sedation drugs.

Activities Requiring Mental Alertness

Advise patients that performance of activities requiring mental alertness, such as operating a motor vehicle or using hazardous machinery or signing legal documents, may be impaired for some time after general anesthesia.

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