

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-244

LABELING

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

LUSEDRA (fospropofol disodium) Injection, for intravenous use

Initial U.S. Approval: 20XX

-----INDICATIONS AND USAGE-----

LUSEDRA is a sedative-hypnotic agent indicated for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures.(1)

-----DOSAGE AND ADMINISTRATION-----

- Use supplemental oxygen in all patients undergoing sedation with LUSEDRA (2.1). Continuously monitor with pulse oximetry, electrocardiogram, and frequent blood pressure measurements (5.1).
- **Standard dosing regimen:** initial intravenous bolus dose of 6.5 mg/kg followed by supplemental doses of 1.6 mg/kg as needed. No initial dose should exceed 16.5 mL; no supplemental dose should exceed 4 mL. (2.2)
- **Modified dosing regimen** [for patients who are ≥65 years of age or who have severe systemic disease (ASA P3 or P4)]: 75 % of the standard dosing regimen. (2.3)
- Administer supplemental doses only when patients can demonstrate purposeful movement in response to verbal or light tactile stimulation and no more frequently than every 4 minutes. (2.1)
- Adults who weigh >90 kg should be dosed as if they are 90 kg; adults who weigh <60 kg should be dosed as if they are 60 kg. (2.2)
- Intended for single use administration only.

-----DOSAGE FORMS AND STRENGTHS-----

Injection, solution containing 1,050 mg fospropofol disodium per 30 mL. (3)

-----CONTRAINDICATIONS-----

None

-----WARNINGS AND PRECAUTIONS-----

- A person trained in the administration of general anesthesia and not involved in the conduct of the diagnostic/therapeutic procedure should manage treatment of patients with LUSEDRA. (5.1)
- Respiratory depression (5.2)
- Hypoxemia (5.3)
- Hypotension (5.4)

-----ADVERSE REACTIONS-----

Most common adverse reactions (> 20 %) are paresthesia and pruritus. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai, Inc. at 1-888-422-4743 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

As with other sedative-hypnotic agents, LUSEDRA may produce additive cardio-respiratory effects when administered with other cardio-respiratory depressants such as benzodiazepines and narcotic analgesics. (7)

-----USE IN SPECIFIC POPULATIONS-----

- Patients ≥65 years of age should receive the modified dosing regimen. (2.3, 8.5)
- Patients with severe systemic disease (ASA P3 or P4) should receive the modified dosing regimen. (2.3)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUSEDRA™ (fospopofol disodium) injection is an intravenous sedative-hypnotic agent indicated for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

- Administer LUSEDRA intravenously as a bolus injection.
- Use supplemental oxygen for all patients undergoing sedation with LUSEDRA.
- Individualize the dosage of LUSEDRA and titrate to the level of sedation required for the procedure.
- In adults aged 18 to <65 years who are healthy or have mild systemic disease as categorized by the American Society of Anesthesiology (ASA P1 or P2), the standard dosing regimen of LUSEDRA should be followed [see *Standard Dosing Regimen for Sedation* (2.2)].
- In adults who are ≥ 65 years of age or who have severe systemic disease (ASA P3 or P4), the modified dosing regime should be followed [see *Modified Dosing Regimen for Sedation in Patients ≥ 65 years or Those with Severe Systemic Disease* (2.3)].
- Administer supplemental doses of LUSEDRA based on the patient's level of sedation and the level of sedation required for the procedure. Give supplemental doses only when patients can demonstrate purposeful movement in response to verbal or light tactile stimulation and no more frequently than every 4 minutes. Use only the minimum dosage required to facilitate the procedure.
- Consider the potential for worsened cardio-respiratory depression prior to using LUSEDRA concomitantly with other drugs that have the same potential (e.g., sedative-hypnotics or narcotic analgesics) [see *Warnings and Precautions* (5.2, 5.3)].
- In clinical studies, an opioid premedication (fentanyl citrate 50 mcg intravenously) was administered five minutes prior to the initial dose of LUSEDRA.

2.2 Standard Dosing Regimen for Sedation

In adults aged 18 to <65 years who are healthy or have mild systemic disease (ASA P1 or P2)¹, the standard dosing regimen of LUSEDRA is an initial intravenous bolus of 6.5 mg/kg followed by supplemental doses of 1.6 mg/kg intravenous (25 % of initial dosage) as needed to achieve the desired level of sedation as shown in Table 1.

The dosage of LUSEDRA is limited by lower and upper weight bounds of 60 kg and 90 kg. Adults who weigh >90 kg should be dosed as if they weigh 90 kg. **No initial dose should exceed 16.5 mL; no supplemental dose should exceed 4 mL.** Adults who weigh <60 kg should be dosed as if they weigh 60 kg. Dosages lower than those specified for the lower weight limit may be used to achieve lesser levels of sedation. In clinical studies, an opioid premedication (fentanyl citrate 50 mcg IV) was administered five minutes prior to the initial dose of LUSEDRA.

Table 1. Standard Dosing Regimen, Adults 18 to <65 Years of Age Who are Healthy or Have Mild Systemic Disease (ASA P1 or P2)

Weight (kg)	Initial Dose		Supplemental Dose No more frequently than every 4 min	
	mg	mL	mg	mL
≤60	385	11	105	3
61 to 63	402.5	11.5	105	3

64 to 65	420	12	105	3
66 to 68	437.5	12.5	105	3
69 to 71	455	13	105	3
72 to 74	472.5	13.5	122.5	3.5
75 to 76	490	14	122.5	3.5
77 to 79	507.5	14.5	122.5	3.5
80 to 82	525	15	140	4
83 to 84	542.5	15.5	140	4
85 to 87	560	16	140	4
88 to 89	577.5	16.5	140	4
≥90	577.5	16.5	140	4
Doses in this table are rounded to the nearest half-milliliter volume to facilitate practical measurement, hence may differ slightly from the dose recommended on the basis of mg/kg.				

2.3 Modified Dosing Regimen for Sedation in Patients ≥65 years or Those with Severe Systemic Disease (ASA P3 or P4)

Adults ≥65 years of age or those with severe systemic disease (ASA P3 or P4)¹ should receive initial and supplemental intravenous dosages of 75 % of the standard dosing regimen, as presented in Table 2. LUSEDRA is administered intravenously as a bolus injection. In clinical studies, an opioid premedication (fentanyl citrate 50 mcg IV) was administered five minutes prior to the initial dose of LUSEDRA.

Table 2. Modified Dosing Regimen, Ages ≥ 65 Years Or Those with Severe Systemic Disease (ASA P3 or P4)

Weight (kg)	Initial Dose		Supplemental Dose No more frequently than every 4 min	
	mg	mL	mg	mL
≤60	297.5	8.5	70	2
61 to 62	297.5	8.5	70	2
63 to 64	315	9	87.5	2.5
65 to 66	315	9	87.5	2.5
67 to 69	332.5	9.5	87.5	2.5
70 to 73	350	10	87.5	2.5
74 to 77	367.5	10.5	87.5	2.5
78 to 80	385	11	105	3

81 to 84	402.5	11.5	105	3
85 to 87	420	12	105	3
88 to 89	437.5	12.5	105	3
≥90	437.5	12.5	105	3
<p>Note: Doses in this table are rounded to the nearest half-milliliter volume to facilitate practical measurement, hence may differ slightly from the dose recommended on the basis of mg/kg.</p>				

2.4 Preparation

LUSEDRA is provided as a ready to use formulation intended for single-patient use only. Prepare LUSEDRA following strict aseptic techniques. Draw LUSEDRA into sterile syringes immediately after vials are opened. Discard any unused portion at the end of the procedure.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if there is evidence of particulate matter or discoloration.

LUSEDRA has been shown to be compatible with the following fluids:

- 5 % Dextrose Injection, USP
- 5 % Dextrose and 0.2 % Sodium Chloride, USP
- 5 % Dextrose and 0.45 % Sodium Chloride Injection, USP
- 0.9 % Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP
- Lactated Ringer's and 5 % Dextrose Injection, USP
- 0.45 % Sodium Chloride Injection, USP
- 5 % Dextrose, 0.45 % NaCl and 20 mEq KCl, USP

Do not mix LUSEDRA with other drugs or fluids prior to administration. LUSEDRA is not physically compatible with midazolam HCl or meperidine HCl, and compatibility with other agents has not been adequately evaluated.

Administer LUSEDRA through a secure, freely flowing, peripheral intravenous line using commonly available intravenous administration sets. Flush the infusion line with normal saline before and after administration of LUSEDRA.

LUSEDRA is not light sensitive. LUSEDRA does not need to be filtered before use.

3 DOSAGE FORMS AND STRENGTHS

Single-use vial contents: Solution for intravenous administration containing 35 mg of fospropofol disodium per mL (1,050 mg of fospropofol disodium in 30 mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Monitoring

LUSEDRA should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the diagnostic or therapeutic procedure. Sedated patients should be continuously monitored, and facilities for maintenance of a patent airway, providing artificial ventilation, administering supplemental oxygen, and instituting cardiovascular resuscitation must be immediately available. Patients should be continuously monitored during sedation and through the recovery process for early signs of hypotension, apnea, airway obstruction, and/or oxygen desaturation.

5.2 Respiratory Depression

LUSEDRA may cause loss of spontaneous respiration. Apnea was reported in 1/455 (< 1 %) patients treated with LUSEDRA using the standard or modified dosing regimen [see *Dosage and Administration* (2.2, 2.3)]. In patients treated with greater than the recommended LUSEDRA dose, apnea was reported in 14/556 (3 %).

Supplemental oxygen is recommended for all patients receiving LUSEDRA. Dosages of LUSEDRA must be individualized for each patient and titrated to effect [see *Dosage and Administration* (2.1) and *Clinical Pharmacology* (12.2)]. Use lower doses of LUSEDRA in patients who are ≥ 65 years of age or who have severe systemic disease [see *Dosage and Administration* (2.3)]. The additive cardio-respiratory effects of narcotic analgesics and sedative-hypnotic agents should be considered when administered concomitantly with LUSEDRA.

Patients should be assessed for their ability to demonstrate purposeful response while sedated with LUSEDRA as patients who are unable to do so may lose protective reflexes. Airway assistance maneuvers may be required in the management of respiratory depression (see Table 4).

5.3 Hypoxemia

LUSEDRA may cause hypoxemia detectable by pulse oximetry. Hypoxemia was reported in 20/455 (4 %) patients treated with LUSEDRA using the standard or modified dosing regimen [see *Dosage and Administration* (2.2, 2.3)]. Hypoxemia was reported among patients who retained the ability to respond purposefully to their health care provider following administration of LUSEDRA. Therefore, retention of purposeful responsiveness did not prevent patients from becoming hypoxemic following administration of LUSEDRA. In patients treated with greater than the recommended LUSEDRA dose, hypoxemia was reported in 151/556 (27 %).

The risk of hypoxemia is reduced by appropriate positioning of the patient, and the use of supplemental oxygen in all patients receiving LUSEDRA. Airway assistance maneuvers may be required in the management of hypoxemia (see Table 4). The additive cardio-respiratory effects of narcotic analgesics and other sedative-hypnotic agents should be considered when administered concomitantly with LUSEDRA.

5.4 Patient Unresponsiveness to Vigorous Tactile or Painful Stimulation

LUSEDRA has not been studied for use in general anesthesia. However, administration of LUSEDRA may inadvertently cause patients to become unresponsive or minimally responsive to vigorous tactile or painful stimulation. The incidence of patients sedated for colonoscopy who became minimally responsive or unresponsive to vigorous tactile or painful stimulation was 7/183 (4%). The duration of minimal or complete unresponsiveness in colonoscopy patients ranged from 2 to 16 minutes. Among patients sedated for bronchoscopy, the incidence of patients who became minimally or completely unresponsive to vigorous tactile or painful stimulation was 24/149 (16%). The duration of minimal to complete unresponsiveness in bronchoscopy patients ranged from 2 to 20 minutes.

5.5 Hypotension

Hypotension following the use of LUSEDRA may occur. Hypotension was reported in 18/455 (4 %) patients treated with LUSEDRA using the standard or modified dosing regimen [see *Dosage and Administration* (2.2, 2.3)]. In patients treated with greater than the recommended LUSEDRA dose, hypotension was reported in 31/556 (6 %).

Patients with compromised myocardial function, reduced vascular tone, or who have reduced intravascular volume may be at an increased risk for hypotension. A secure intravenous access catheter and supplemental volume replacement fluids should be readily available during the procedure. Additional pharmacological management may be necessary.

6 ADVERSE REACTIONS

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

- Respiratory depression [see *Warnings and Precautions (5.2)*]
- Hypoxemia [see *Warnings and Precautions (5.3)*]
- Loss of purposeful responsiveness [see *Warnings and Precautions (5.4)*]
- Hypotension [see *Warnings and Precautions (5.5)*]

The most common adverse reactions (reported in greater than 20%) are paresthesia and pruritus.

The most commonly reported reasons for discontinuation are paresthesia and cough.

6.1 Clinical Trials Experience

Adverse reactions presented in this section are derived from 332 patients in 3 controlled clinical trials in patients undergoing colonoscopy or flexible bronchoscopy and 123 patients in one open-label study in patients undergoing minor procedures. Patients enrolled in the studies who received the standard or modified dosing regimen included males and females, ≥ 18 years of age and ranging from healthy (359/455 [79 %] ASA P1 or P2) to those with severe systemic disease (96/455 [21 %] ASA P3 or P4). Of the 455 patients enrolled, 345 (76 %) were ≥ 18 to < 65 years of age and 110 (24 %) were ≥ 65 years of age. Adverse reactions are reported for patients who received the standard or the modified dosing regimen [see *Dosage and Administration (2)*]. The majority of procedures were less than thirty minutes in duration. All patients in these studies received 50 mcg fentanyl citrate intravenous as premedication and some of the patients received additional 25 mcg fentanyl citrate supplemental doses. Adverse reactions occurring in ≥ 2 % of patients in these studies are presented in Table 3.

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 accurately reflect the rates observed in practice.

Table 3. Common Adverse Reactions for Patients Receiving the Standard or Modified Dosing Regimen (Reactions Occurring at a Rate ≥ 2 %)

Reaction Term	Colonoscopy (N=183) n (%)	Minor Procedures (N=123) n (%)	Bronchoscopy (N=149) n (%)
Gastrointestinal disorders			
Nausea	0	5 (4)	2 (1)
Vomiting	0	4 (3)	0
Injury, poisoning, and procedural complications			
Procedural Pain	0	0	3 (2)
Nervous system disorders			
Paresthesia ^a	135 (74)	77 (63)	78 (52)
Headache	1 (1)	3 (2)	1 (1)
Respiratory, thoracic, and mediastinal disorders			
Hypoxemia	3 (2)	1 (1)	16 (11)
Skin and subcutaneous tissue disorders			
Pruritus ^b	30 (16)	34 (28)	24 (16)
Vascular disorders			

Hypotension	4 (2)	4 (3)	10 (7)
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^aParesthesia includes the following terms: Paresthesia genital male; Burning sensation; Genital burning sensation; Vaginal burning sensation; Skin burning sensation; Genital pain (reported as burning); Perineal pain (reported as burning); Anal discomfort (reported as burning); Chest pain (reported as burning); Ear discomfort (reported as burning); Nasal discomfort (reported as burning); Buttock pain (reported as stinging); Groin pain (reported as stinging); Pain (reported as stinging); Sensory disturbance (reported as non-specific sensation in pubic area).

^bPruritus includes the following terms: Genital pruritus female; Genital pruritus male; Pruritus genital; Pruritus ani; Pruritus generalized

Paresthesias (including burning, tingling, stinging) and/or pruritus, usually manifested in the perineal region, were the most frequently recorded adverse reactions in clinical trials. Paresthesias and pruritus generally occurred within 5 minutes after administration of the initial dose of LUSEDRA and were generally transient and mild to moderate in intensity. The pharmacologic basis of these sensory phenomena is unknown. No pretreatments, including the use of nonsteroidal anti-inflammatory drugs, opioids, or lidocaine, are known to have an effect on, or to reduce the incidence of these sensations.

Sedation-related adverse reactions were experienced at the following rates for subjects receiving the standard or modified LUSEDRA dosing regimen: 20/455 (4 %) hypoxemia, 18/455 (4 %) hypotension, 1/455 (< 1 %) apnea. A greater rate of sedation-related adverse reactions necessitating intervention was observed in patients undergoing bronchoscopy compared with colonoscopy and minor surgical procedures. In the colonoscopy studies, 5/183 (3 %) patients were ASA P3. In the minor surgical procedures study, 23/123 (19 %) patients were ASA P3 or P4. In the flexible bronchoscopy study, 68/150 (46 %) patients were ASA P3 or P4. The type and incidence of airway assistance interventions required for patients who experienced sedation-related adverse reactions are presented in Table 4.

Table 4. Patient Incidence of Airway Management Events

	Healthy Subjects ^a	Colonoscopy ^b	Minor Procedures ^b	Flexible Bronchoscopy ^b
	6 mg/kg N=69 n (%)	6.5 mg/kg (or modified dosing regimen) N=183 n (%)	6.5 mg/kg (or modified dosing regimen) N=123 n (%)	6.5 mg/kg (or modified dosing regimen) N=149 n (%)
Increased O ₂	0	0	0	21 (14)
Patient Repositioning	0	0	0	2 (1)
Verbal Stimulation	0	2 (1)	1 (1)	5 (3)
Tactile Stimulation	0	0	0	3 (2)
Face Mask (100 % O ₂)	0	0	0	1 (1)
Jaw Thrust	0	0	0	2 (1)
Chin Lift	0	0	1 (1)	3 (2)
Nasal Trumpet	0	0	0	0
Oral Airway	0	0	0	0
Suction	0	0	0	2 (1)
Manual Ventilation (bag valve mask)	0	0	0	1 (1)
Mechanical Ventilation	0	0	0	0

^a No concomitant medications administered. All subjects were healthy volunteers.

^b All patients premedicated with 50 mcg fentanyl citrate. Subjects ranged from healthy to those with severe systemic disease that is a constant threat to life (ASA P1 to P4).

6.2 Adverse Reactions in Prolonged Exposure in Adults

The safety of LUSEDRA for continuous sedation has not been established and therefore its use is not recommended. LUSEDRA was administered to 38 intubated and mechanically ventilated patients in post-operative and intensive care settings. An occurrence of nonsustained ventricular tachycardia was observed as a serious adverse reaction in one patient in the study. Another patient with acute myeloid leukemia with renal and hepatic insufficiency experienced a further increase in plasma formate concentration from a baseline of 66 mcg/mL to a post-dose level of 212 mcg/mL after a 12-hour infusion. The clinical significance of these findings is unknown.

7 DRUG INTERACTIONS

LUSEDRA may produce additive cardio-respiratory effects when administered with other cardio-respiratory depressants such as sedative-hypnotics and narcotic analgesics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects:

Pregnancy Category B.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Reproduction studies have been performed in rats and rabbits at doses up to 0.6 and 1.7 times the anticipated human dose for a procedure of 16 minutes based on a comparison of doses expressed as mg/m² and have revealed no evidence of impaired fertility or harm to the fetus due to LUSEDRA.

Pregnant rats were treated with fospropofol disodium (5, 20, or 45 mg/kg/day, IV) from gestation day 7 through 17 (the highest dose is 0.6 times the anticipated human dose for a procedure of 16 minutes based on a comparison of doses expressed as mg/m²). Doses of 20 and 45 mg/kg/day produced significant maternal toxicity. No drug-related adverse effects on embryo-fetal development were noted.

Pregnant rabbits were treated with fospropofol disodium (14, 28, 56 or 70 mg/kg/day, IV) from gestation day 6 through 18 (the highest dose is 1.7 times the anticipated human dose for a procedure of 16 minutes based on a comparison of doses expressed as mg/m²). Significant maternal toxicity was noted at all doses. No drug-related adverse effects on embryo-fetal development were noted.

Nonteratogenic effects.

Pregnant rats were administered 0, 5, 10, or 20 mg/kg/day fospropofol disodium from gestation day 7 through lactation day 20 to evaluate perinatal and postnatal development (the highest dose is 0.2 times the anticipated human dose for a procedure of 16 minutes based on a comparison of doses expressed as mg/m²). There were no clear treatment-related effects on growth, development, behavior (passive avoidance and water maze) or fertility and mating capacity of the offspring.

8.2 Labor and Delivery

LUSEDRA is not recommended for use in labor and delivery, including Cesarean section deliveries. It is not known if fospropofol crosses the placenta; however, propofol is known to cross the placenta, and as with other sedative-hypnotic agents, the administration of LUSEDRA may be associated with neonatal respiratory and cardiovascular depression.

8.3 Nursing Mothers

It is not known whether fospropofol is excreted in human milk; however, propofol has been reported to be excreted in human milk and the effects of oral absorption of fospropofol or propofol are not known. LUSEDRA is not recommended for use in nursing mothers.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established because LUSEDRA has not been studied in persons <18 years of age. LUSEDRA is not recommended for use in this population.

8.5 Geriatric Use

In studies of LUSEDRA for sedation in brief diagnostic and therapeutic procedures, 17 % patients were ≥ 65 years of age and 5 % of patients were ≥ 75 years of age. Patients ≥ 65 years of age should receive the modified dosing regimen [see *Dosage and Administration* (2.3)]. Hypoxemia was reported more frequently among patients aged ≥ 75 years than among patients aged 65 to <75 years and less frequently among younger patients, aged 18 to <65 years.

8.6 Patients with Renal Impairment

In studies of LUSEDRA for sedation in brief diagnostic and therapeutic procedures, 21 % of patients had a creatinine clearance <80 mL/min and 4 % had a creatinine clearance <50 mL/min. Pharmacokinetics of fospropofol or propofol were not altered in patients with mild to moderate renal insufficiency. No dosing adjustments are required for patients with creatinine clearance ≥ 30 mL/min. Limited safety and efficacy data are available for LUSEDRA in patients with creatinine clearance <30 mL/min.

8.7 Patients with Hepatic Impairment

LUSEDRA has not been adequately studied in patients with hepatic impairment. Caution should be exercised when using fospropofol disodium in patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Abuse

No formal studies of the abuse potential of LUSEDRA have been conducted. Administration of LUSEDRA resulted in euphoria in a small number of subjects who received intravenous or oral dosing.

9.2 Dependence

No formal studies of dependence have been conducted.

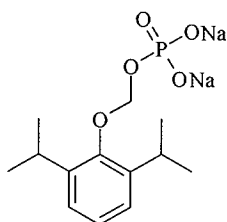
10 OVERDOSE

Overdosage with LUSEDRA can cause cardiorespiratory depression. If overdosage occurs, LUSEDRA administration should be discontinued immediately. Respiratory depression may require manual or mechanical ventilation. Cardiovascular depression may require elevation of lower extremities, intravascular volume replacement, and/or pharmacological management.

Formate and phosphate are metabolites of LUSEDRA and may contribute to signs of toxicity following overdosage. Signs of formate toxicity are similar to those of methanol toxicity and are associated with anion-gap metabolic acidosis. Intravenous exposure to a large amount of phosphate could potentially cause hypocalcemia with paresthesia, muscle spasms, and seizures.

11 DESCRIPTION

LUSEDRA is an injection solution intended for intravenous administration as a sedative-hypnotic agent. LUSEDRA is an aqueous, sterile, nonpyrogenic, clear, colorless, iso-osmotic solution containing 35 mg/mL of fospropofol disodium. Fospropofol disodium is a water-soluble prodrug of propofol, chemically described as 2,6-diisopropylphenoxymethyl phosphate, disodium salt. The structural and molecular formulas are shown in Figure 1.



Molecular Formula: C₁₃H₁₉O₅PNa₂

Molecular Weight: 332.24

Figure 1. Structural and Molecular Formulas of Fospropofol Disodium

The inactive components include, monothioglycerol (0.25 wt%) and tromethamine (0.12 wt%). LUSEDRA has a pH of 8.2 to 9.0. LUSEDRA does not contain any antimicrobial preservatives and is intended for single-use administration.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fospropofol disodium is a prodrug of propofol. Following intravenous injection, fospropofol is metabolized by alkaline phosphatases. For every millimole of fospropofol disodium administered, one millimole of propofol is produced (1.86 mg of fospropofol disodium is the molar equivalent of 1 mg propofol).

12.2 Pharmacodynamics

The pharmacology of fospropofol, once metabolized to propofol, is comparable to that of propofol lipid emulsion, however, the liberation of propofol from fospropofol results in differences in the timing of the pharmacodynamic effects. To characterize the pharmacokinetic/pharmacodynamic (PK/PD) profile of propofol derived from LUSEDRA, 12 healthy subjects were administered a 10 mg/kg intravenous bolus dose of LUSEDRA and the sedative effect was measured as a decrease in Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score (Table 5).² The PK and PD results are shown in Figure 2. Peak plasma levels of propofol (2.2 ± 0.4 µg/mL) released from fospropofol were noted by 8 min (range 4 - 13 min) and minimum mean MOAA/S score of 1.2 (range 0 - 3) was noted in 7 min (range 1 - 15). Subjects completely recovered from sedative effects between 21 - 45 minutes after LUSEDRA administration.

Table 5. Modified Observer's Assessment of Alertness/Sedation Scale²

Responsiveness	Score
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

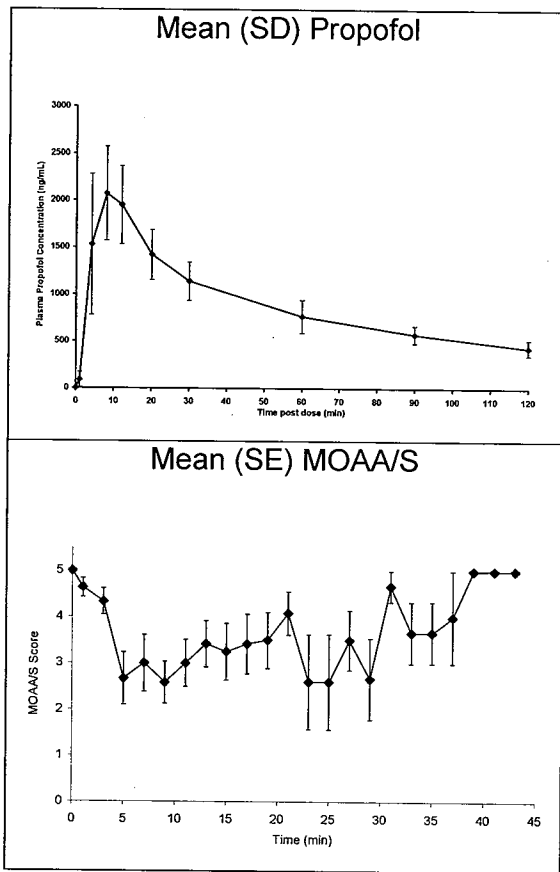


Figure 2. Pharmacokinetic and Pharmacodynamic Profiles after a 10 mg/kg Bolus Dose of LUSEDRA

LUSEDRA was evaluated in randomized, blinded, dose-controlled studies for sedation in patients undergoing colonoscopy and flexible bronchoscopy [see *Clinical Studies (14.1)*]. Figure 3 shows MOAA/S scores over time in each of the studies for those patients who received the standard and modified dosing regimens. In the study of patients undergoing colonoscopy, patients who received the standard and modified dosing regimens had a median [range] time to sedation (time from first dose of sedative to the first of 2 consecutive MOAA/S scores of ≤ 4) of 8.0 [2, 28] minutes and a median time to Fully Alert (3 consecutive responses to their name spoken in a normal tone, measured every 2 minutes beginning at or after the end of the procedure) of 5.0 [0, 47] minutes. In the study of patients undergoing flexible bronchoscopy, patients who received the standard and modified LUSEDRA dosing regimens had a median time to sedation of 4 [2, 22] minutes and a median time to Fully Alert of 5.5 [0, 61] minutes.

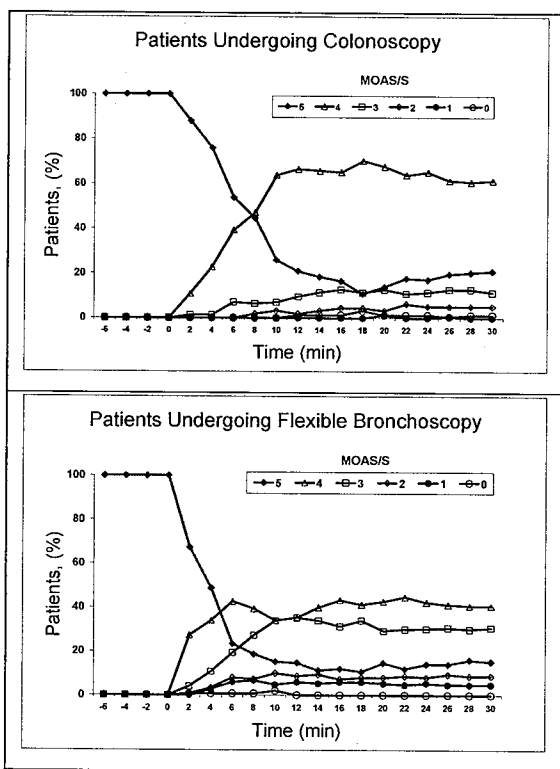


Figure 3. Percentage of Patients at Each MOAA/S Score Over Time

Within the recommended dose range, there were no differences in matched QTc interval changes between LUSEDRA and placebo. The effect of LUSEDRA on the QTcF interval was measured in a crossover study in which healthy subjects (n=68) received the following treatments: 6 mg/kg intravenous LUSEDRA; 18 mg/kg intravenous LUSEDRA; moxifloxacin 400 mg orally (positive control); and normal saline IV. After baseline and placebo adjustment, the maximum mean QTcF change was 2 ms (1-sided 95% Upper CI: 6 ms) for the 6 mg/kg dose and 8 ms (1-sided 95% Upper CI: 12 ms) for the 18 mg/kg dose. Used as a positive control, moxifloxacin had a maximum mean change in QTcF of 12 ms (1-sided 95% Lower CI: 6 ms).

12.3 Pharmacokinetics

PK parameters were evaluated in a cross-over study of 68 healthy subjects, 18 to 45 years of age, who received 6 and 18 mg/kg intravenous bolus doses of LUSEDRA. PK parameters are shown in Table 5. The C_{max} and $AUC_{0-\infty}$ values of fospropofol were dose proportional. The intersubject variability in C_{max} and $AUC_{0-\infty}$ was low. Propofol was rapidly liberated reaching plasma C_{max} at a median T_{max} of 12 minutes for LUSEDRA 6 mg/kg and 8 minutes for LUSEDRA 18 mg/kg. Concentration-time profiles showed a biexponential decline. The increase in C_{max} and $AUC_{0-\infty}$ of propofol was dose proportional.

Table 5. Pharmacokinetics Parameters (mean±SD) for Fospropofol and Propofol from LUSEDRA Administration

Parameter	Fospropofol			Propofol from LUSEDRA		
	Healthy (6 mg/kg) N=68	Healthy (18 mg/kg) N=68	Patient (6.5 mg/kg) N=667	Healthy (6 mg/kg) N=68	Healthy (18 mg/kg) N=68	Patient (6.5 mg/kg) N=400
C_{max} (mcg/mL)	78.7±15.4	211±48.6	--	1.08±0.33	3.90±0.822	--

T _{max} (min)	4	2	--	12	8	--
AUC _{0-∞} (mcg·h/mL)	19.2±3.59	50.3±8.4	19.0±7.2	1.70±0.29	5.67±1.28	1.2±0.39
CL _p (L/h/kg)	0.28±0.053	0.32±0.058	0.36±0.16	1.95±0.34	1.79±0.39	3.2±0.92
t _{1/2} (h)	0.81±0.08	0.81±0.09	0.88±0.08	2.06±0.77	1.76±0.54	1.13±0.28

Distribution

Fospropofol has a low volume of distribution of 0.33±0.069 L/kg and the liberated propofol has a large volume of distribution (5.8 L/kg).

Both fospropofol and its active metabolite propofol are highly protein bound (approximately 98 %), primarily to albumin. Fospropofol does not affect the binding of propofol to albumin.

Metabolism

Fospropofol is completely metabolized by alkaline phosphatases to propofol, formaldehyde, and phosphate. Formaldehyde and phosphate plasma concentrations are comparable to endogenous levels when fospropofol disodium is administered as recommended. Formaldehyde is further metabolized to formate by several enzyme systems, including formaldehyde dehydrogenase, present in various tissues. Propofol liberated from fospropofol is further metabolized to major metabolites propofol glucuronide (34.8 %), quinol-4-sulfate (4.6 %), quinol-1-glucuronide (11.1 %), and quinol-4-glucuronide (5.1 %). Oxidation to CO₂ is the primary means of eliminating excess formate.

Fospropofol is not a substrate of CYP450 enzymes.

Elimination

After a single 400 mg intravenous dose of [¹⁴C]-fospropofol disodium in humans, approximately 71 % of radioactivity was recovered in the urine within 192 hours. Total body clearance (CL_p) of fospropofol was 0.280±0.053 L/h/kg and renal elimination of fospropofol was insignificant (<0.02 % of dose). The terminal phase elimination half-life (t_{1/2}) of fospropofol was 0.81±0.08 and 0.88±0.08 hours in healthy subjects and patients, respectively. In healthy subjects, the apparent total body clearance of liberated propofol (CL_p/F) was 1.95±0.345 L/h/kg and t_{1/2} was 2.06±0.77 hours. In patients, the CL_p of fospropofol was 0.31±0.14 L/h/kg and CL_p/F for propofol was 2.74±0.80 L/h/kg and is similar to that observed in healthy subjects.

Special Populations

Population pharmacokinetic analysis indicated no influence of race, gender, age, renal impairment or alkaline phosphatase concentrations on the pharmacokinetics of fospropofol. Pharmacokinetics of propofol derived from fospropofol was not influenced by race, gender, or renal impairment.

LUSEDRA has not been adequately studied in patients with hepatic impairment. Caution should be exercised when using fospropofol disodium in patients with hepatic impairment.

Drug Interactions

There was no effect of analgesic premedication [fentanyl (1 mcg/kg); meperidine (0.75 mg/kg); midazolam (0.01 mg/kg); morphine (0.1 mg/kg)] on plasma pharmacokinetics of fospropofol.

In an in vitro protein binding study there was no significant interaction between fospropofol and propofol at concentrations up to 200 mcg/mL and 5 mcg/mL, respectively. The interaction of fospropofol with other highly protein-bound drugs given concomitantly has not been studied.

Potential of fospropofol or its major metabolite, propofol, to inhibit or induce major cytochrome P450 enzymes is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis:

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of fospropofol disodium.

Mutagenesis:

Fospropofol was not genotoxic in the Ames bacterial reverse mutation assay, with or without metabolic activation, and in the in vivo mouse micronucleus assay. Fospropofol was positive in the L5178Y TK⁺/ mouse lymphoma forward mutation assay in the presence of metabolic activation. In contrast, fospropofol was negative in this assay in the presence of formaldehyde-metabolizing enzymes suggesting that the positive finding is likely due to an artifact of the culture conditions.

Impairment of Fertility:

Male rats were treated with 5, 10, or 20 mg/kg fospropofol for 4 weeks prior to mating. Male fertility was not altered in animals treated with 20 mg/kg (0.3-fold the total human dose for a procedure of 16 minutes based on a mg/m² basis).

Female rats were treated with 5, 10, or 20 mg/kg fospropofol for two weeks prior to mating. There were no clear treatment-related effects on female fertility at a dose of 20 mg/kg (0.3-fold the total human dose for a procedure of 16 minutes based on a mg/m² basis).

14 CLINICAL STUDIES

14.1 Use in Sedation for Diagnostic or Therapeutic Procedures

The standard and modified LUSEDRA dosing regimens were evaluated in two controlled studies in patients dosed with LUSEDRA who were over 18 years of age and undergoing diagnostic or therapeutic procedures. All patients received 50 mcg of fentanyl citrate intravenously before study sedative medication. The primary endpoint was the rate of "sedation success," defined as the proportion of patients who did not respond readily to their name spoken in a normal tone of voice (Modified Observer's Assessment of Alertness/Sedation Scale score of 4 or less) on 3 consecutive measurements taken every 2 minutes and who completed the procedure without the use of alternative sedative medication and without the use of manual or mechanical ventilation.²

In both studies, an initial bolus dose and up to 3 supplemental doses at 25 % of the initial bolus of study sedative medication was administered intravenously to sedate patients so that they did not respond readily to their name spoken in a normal tone and to allow the investigator to start the procedure. During the procedure supplemental doses at 25 % of the initial bolus were allowed to maintain sedation. Patients who were not adequately sedated with study drug received alternative sedative medication per the site's standard of care; however, sites were instructed not to use propofol as it would interfere with PK measurements.

The standard and modified LUSEDRA dosing regimens were evaluated in a randomized, blinded, dose-controlled study for sedation in patients undergoing colonoscopy. All of the patients who received alternative sedative medication (n=19) received midazolam. Patients randomized to receive the LUSEDRA standard or modified dosing regimen had a sedation success rate of 87% and required a mean number of supplemental doses of 2.3 (± 1.4 SD). Patients randomized to receive LUSEDRA had median procedure durations of 11 minutes.

The standard and modified LUSEDRA dosing regimens were also evaluated in a randomized, blinded, dose-controlled study for sedation in patients undergoing flexible bronchoscopy. All of the patients who received alternative sedative medication (n=12), received midazolam. Patients randomized to receive the LUSEDRA standard or modified dosing regimen had a sedation success rate of 89 % and required a mean number of supplemental doses of 1.7 (± 1.6 SD). Patients randomized to LUSEDRA had a median procedure duration of 10 minutes.

15 REFERENCES

1. Kost, Michael. Moderate Sedation/Analgesia: Core Competencies for Practice. Elsevier Health Sciences, 2004. pp 62-63.
2. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol*. 1990; 10(4):244-51.

16 HOW SUPPLIED/STORAGE AND HANDLING

LUSEDRA, 35 mg/mL (total of 1,050 mg/30 mL) fospropofol disodium, is supplied as a single-use, aqueous, sterile, nonpyrogenic, clear, colorless solution in glass vials ready for intravenous injection. Each vial is filled with 32.1 mL intended to deliver a minimum of 30 mL of fospropofol disodium solution. Store at controlled room temperature 25 °C (77 °F). Excursions permitted between 15° and 30 °C (59 ° and 86 °F).

NDC 62856-350-01.

17 PATIENT COUNSELING INFORMATION

Paresthesias (including burning, tingling, stinging) and/or pruritus, usually manifested in the perineal region are frequently experienced upon injection of the initial dose of LUSEDRA. Inform the patient that these sensations are typically mild to moderate in intensity, last a short time, and require no treatment.

Requirement for a patient escort should be considered. The decision as to when patients who have received LUSEDRA, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, coordination and/or physical dexterity (e.g. operate hazardous machinery, sign legal documents or drive a motor vehicle) must be individualized.

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/s/

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