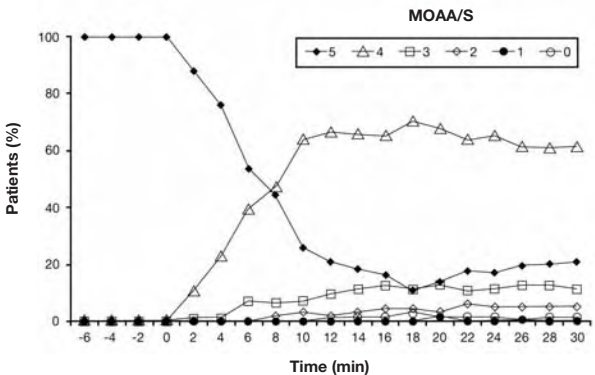


LUSEDRA was evaluated in randomized, blinded, dose-controlled studies for sedation in patients undergoing colonoscopy and flexible bronchoscopy [see *Clinical Studies* (14.1)]. Figure 3 shows MOAA/S scores over time in each of the studies for those patients who received the standard and modified dosing 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.

Patients Undergoing Colonoscopy



Patients Undergoing Flexible Bronchoscopy

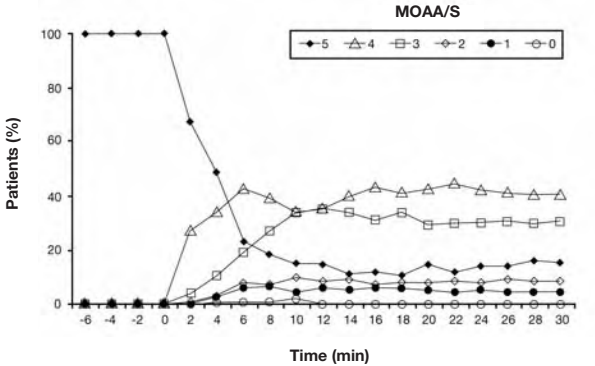


Figure 3. Percentage of Patients at Each MOAA/S Score Over Time

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 crossover 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 6. The C_{max} and AUC_{0-∞} values of fospropofol were dose proportional. The intersubject variability in C_{max} and AUC_{0-∞} 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-∞} of propofol was dose proportional.

Table 6. Pharmacokinetic Parameters (mean±SD) for Fospropofol and Propofol from LUSEDRA Administration			
Fospropofol			
Parameter	Healthy (6 mg/kg) N=68	Healthy (18 mg/kg) N=68	Patient (6.5 mg/kg) N=667
C _{max} (mcg/mL)	78.7±15.4	211±48.6	--
T _{max} (min)	4	2	--
AUC _{0-∞} (mcg•h/mL)	19.2±3.59	50.3±8.4	19.0±7.2
CLp (L/h/kg)	0.28±0.053	0.32±0.058	0.36±0.16
t _{1/2} (h)	0.81±0.08	0.81±0.09	0.88±0.08
Propofol from LUSEDRA			
Parameter	Healthy (6 mg/kg) N=68	Healthy (18 mg/kg) N=68	Patient (6.5 mg/kg) N=400
C _{max} (mcg/mL)	1.08±0.33	3.90±0.822	--
T _{max} (min)	12	8	--
AUC _{0-∞} (mcg•h/mL)	1.70±0.29	5.67±1.28	1.2±0.39
CLp (L/h/kg)	1.95±0.34	1.79±0.39	3.2±0.92
t _{1/2} (h)	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 (CLp) 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 (CLp/F) was 1.95±0.345 L/h/kg and t_{1/2} was 2.06±0.77 hours. In patients, the CLp of fospropofol was 0.31±0.14 L/h/kg, and CLp/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 were 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 a median procedure duration 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

- Kost, M. *Moderate Sedation/Analgesia: Core Competencies for Practice*. Elsevier Health Sciences, 2004: 62-63.
- 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):244-251.

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 62856-350-08

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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7 DRUG INTERACTIONS

LUSEDRA may produce additive cardiorespiratory effects when administered with other cardiorespiratory 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% of 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 Controlled Substance

LUSEDRA is a Schedule IV controlled substance.

9.2 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.

9.3 Dependence

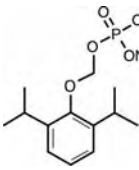
No formal studies of dependence have been conducted.

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-diisopropylphenoxyethyl phosphate, disodium salt. The structural and molecular formulas are shown in Figure 1.



Molecular Formula: C₁₃H₁₉O₆Na₂
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 minutes (range 4-13 minutes) and minimum mean MOAA/S score of 1.2 (range 0-3) was noted in 7 minutes (range 1-15 minutes). Subjects completely recovered from sedative effects between 21 to 45 minutes after LUSEDRA administration.

Table 5. Modified Observer's Assessment of Alertness/Sedation Scale ²	
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

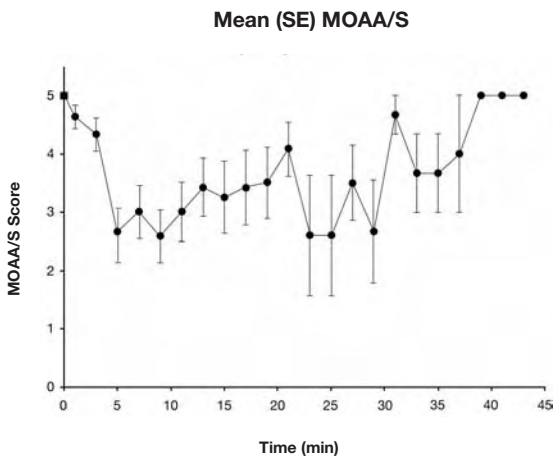
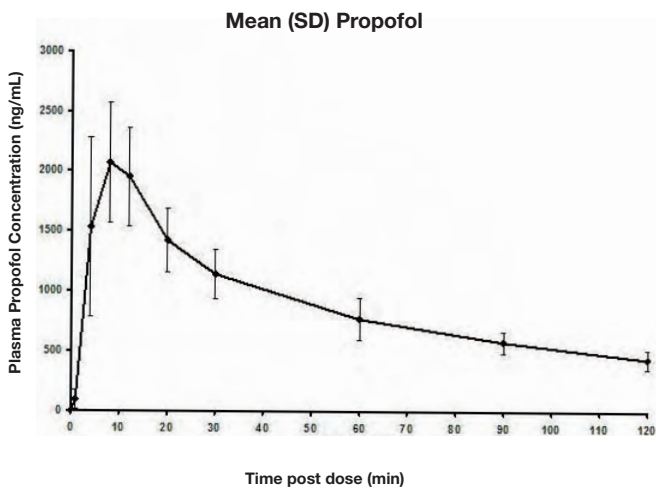


Figure 2. Pharmacokinetic and Pharmacodynamic Profiles after a 10-mg/kg Bolus Dose of LUSEDRA

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Item #:	201219	Revision:	I	Replaces #:	NA	Created on:	9/16/09
Product:	Lusedra	Description:	PI	Designer:	D. Stankiewicz	Package Engineer:	T. Baker
Flat size:	9.5" x 23.75"						
Fonts:	Helvetica Neue Condensed						
PMS Colors:	Black						
Reason for Change:	Product Launch, add CIV symbol, new manuscript (Oct09d), corrections from proofreader's report for Revision H.						



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