

Fospropofol Disodium

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Generic Name:

FOSPROPOFOL DISODIUM

Proprietary Name: *Lusedra* (Eisai)

Approval Rating: S

Therapeutic Class: General

Anesthetics

Similar Drugs: Propofol

Sound- or Look-Alike Names:

Fomepizole, Fosinopril, *Fosrenol*,

Lucentis, Propofol

INDICATIONS

Fospropofol is indicated for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures.¹

CLINICAL PHARMACOLOGY

Fospropofol is a water-soluble phosphate ester prodrug of propofol. Following intravenous (IV) administration, it is rapidly hydrolyzed by alkaline phosphatases to propofol, phosphate, and formaldehyde. Formaldehyde is rapidly converted by aldehyde dehydrogenase to formic acid or formate. Formate is further metabolized to carbon dioxide and water in the presence of tetrahydrofolic acid.² Formaldehyde and phosphate plasma concentrations are comparable with endogenous levels following administration of recommended doses.¹ For every millimole of fos-

propofol disodium administered, 1 millimole of propofol is produced (fospropofol disodium 1.86 mg is the molar equivalent of propofol 1 mg).¹

Propofol is a sedative hypnotic that acts via the release of gamma-aminobutyric acid in the brain.³

PHARMACOKINETICS

The distribution half-life of fospropofol is approximately 6.5 minutes, and the elimination half-life is approximately 46 minutes. The mean residence time is approximately 17 minutes.^{2,4,5} It has been demonstrated that the median time to peak concentration of propofol after administration of fospropofol 6 mg/kg is 12 minutes.¹

It appears that the pharmacokinetics of liberated propofol from fospropofol differ from those of the lipid-formulated propofol in a number of published pharmacokinetic studies; however, issues with the assay used for measuring liberated propofol that may have influenced the results in these studies have been reported recently. Results of these studies should not be used.^{2,4,6} Table 1 summarizes pharmacokinetic information for liberated propofol from a study using newer techniques that is reviewed in the package insert.^{1,6} Both fospropofol and propofol are approximately 98% protein bound, primarily to albumin.¹

The pharmacokinetics of fospropofol are not altered in patients with mild to moderate renal function impairment (creatinine clearance [CrCl] greater than 30

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Table 1. Pharmacokinetics of Fospropofol¹

Parameter	Fospropofol 6.5 mg/kg (n = 667)	Propofol Liberated From Fospropofol 6.5 mg/kg (n = 400)
AUC _{0-∞}	19 mcg•h/mL	1.2 mcg•h/mL
CLp	0.36 L/h/kg	3.2 L/h/kg
Half-life	0.88 h	1.13 h

AUC = area under the curve; CLp = total body clearance.

mL/min). Pharmacokinetic data are not available for patients with CrCl of less than 30 mL/min. The pharmacokinetics of fospropofol have not been assessed in patients with hepatic function impairment.¹ Race, gender, age, and alkaline phosphatase concentrations had no effect on fospropofol pharmacokinetics.¹

COMPARATIVE EFFICACY

The new drug application contained data from several phase 2 and 3 studies of fospropofol in patients undergoing colonoscopy, bronchoscopy, and minor surgical procedures.⁷

Fospropofol was compared with midazolam in a randomized, double-blind, dose-response study enrolling 127 patients. Patients received fospropofol 2, 5, 6.5, or 8 mg/kg or midazolam 0.02 mg/kg following pretreatment with fentanyl 50 mcg. Supplemental doses of study medication were permitted to reach a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) of 4 or less. The mean cumulative doses of fospropofol were 234 mg for the fospropofol 2 mg/kg group, 590 mg for the 5 mg/kg group, 710 mg for the 6.5 mg/kg group, 780 mg for the 8 mg/kg group, and 4.2 mg for the midazolam group; a higher total dose of fentanyl was administered in the patients receiving the lower doses of fospropofol. A dose-dependent increase in sedation suc-

cess was observed. Sedation success—defined as 3 consecutive MOAA/S scores of 4 or less after administration of sedative and completion of the procedure without use of an alternative sedative and without manual or mechanical ventilation—was achieved in 24% of patients in the fospropofol 2 mg/kg group, 35% in the 5 mg/kg group, 69% in the 6.5 mg/kg group, and 96% in the 8 mg/kg group ($P < 0.001$). Additional study results are summarized in Table 2. Memory retention during recovery was greatest in the fospropofol 6.5 mg/kg group. Overall, the 6.5 mg/kg dose reportedly provided the best balance of efficacy and safety in colonoscopy and was selected for further study.^{8,9}

Several additional studies were presented in study abstracts. Fospropofol was evaluated in a double-blind study enrolling 314 patients undergoing colonoscopy. Patients received fospropofol 6.5 mg/kg, fospropofol 2 mg/kg, or midazolam 0.02 mg/kg in a 3:2:1 allocation following pretreatment with fentanyl 50 mcg. Patients weighing less than 60 kg or more than 90 kg received the fospropofol dose of a patient weighing 60 or 90 kg, respectively. Patients 65 years of age and older were prescribed a 25% dose reduction of fospropofol. Patients could receive up to 3 supplemental doses of study drug at 25% of the initial dose every 4

minutes before treatment would be regarded as a failure and an alternative sedative administered. Sedation was assessed using the MOAA/S. The primary end point was sedation success, defined as in the previous study. Results are summarized in Table 3. Midazolam was included in the study as a safety reference; the study was not powered to show differences between fospropofol and midazolam. As in the dose-ranging study, memory retention during recovery was greatest in the 6.5 mg/kg group, likely because of the use of alternative sedatives in the 2 mg/kg group.¹⁰⁻¹³

Fospropofol was also assessed in a small, randomized, open-label study enrolling 20 elderly patients undergoing colonoscopy. Patients older than 65 years of age were randomized for receipt of fospropofol (15 patients) or midazolam (5 patients) following pretreatment with fentanyl 0.5 mcg/kg. Fospropofol 525, 595, or 735 mg or midazolam 0.5, 0.75, or 1 mg was administered based on patient weight. Supplemental doses of study drug and fentanyl were permitted as needed. Sedation success, defined as in the other studies, was achieved in all patients in the fospropofol groups and none in the midazolam group ($P < 0.001$). A single dose of study drug was sufficient for initiation and maintenance of sedation in 13 of the 15 patients treated with fospropofol. The median time to sedation was 2 minutes in the fospropofol group and 12 minutes in the midazolam group. The median time to fully alert was 8 minutes in the fospropofol group and 1 minute in the midazolam group.¹⁴

Fospropofol was further assessed in a randomized, double-blind study enrolling 252 patients who were 22 to 84 years of age

Table 2. Dose-Finding Study of Fospropofol for Sedation in Colonoscopy⁸

<i>Parameter</i>	<i>Fospropofol 2 mg/kg</i>	<i>Fospropofol 5 mg/kg</i>	<i>Fospropofol 6.5 mg/kg</i>	<i>Fospropofol 8 mg/kg</i>	<i>Midazolam 0.02 mg/kg</i>
Sedation success	24%	34.6%	69.2%	95.8%	80.8%
Time to sedation	12.4 min	11 min	6.5 min	4.7 min	5 min
Number of supplemental sedative doses	2.4	2.3	2.1	1.3	3.3
Number of supplemental fentanyl doses	1	0.9	0.7	0.5	0.6
Received alternative sedative	64%	58%	19%	4%	8%
Patients remembering being awake	58.3%	52%	42.3%	33.3%	65.4%
Patients willing to use same product again	80%	84%	96.2%	91.7%	100%
Health care provider satisfaction score, mean	3.5	4.7	6.8	7.7	Not reported
Health care provider satisfaction score of 9 to 10	8%	11.5%	26.9%	50%	11.5%
Health care providers willing to use same product again	24%	57.7%	92.3%	83.3%	76.9%
Time to ready for discharge from end of procedure	15 min	7.8 min	9.1 min	14.2 min	10.2 min

Table 3. Study Results With Fospropofol in Colonoscopy^{10,11}

<i>Parameter</i>	<i>Fospropofol 6.5 mg/kg</i>	<i>Fospropofol 2 mg/kg</i>	<i>Midazolam 0.2 mg/kg</i>
Sedation success	87% ^a	26%	69%
Supplemental analgesic required	55% ^a	77%	Not reported
Patients remembering being awake during procedure	47.5%	55.9%	55.8%
Patients willing to use same product again	95.6%	91.2%	92.3%
Health care provider satisfaction scores at end of procedure, median	9 ^a	4	7

^a*P* ≤ 0.001 vs fospropofol 2 mg/kg.

and who were undergoing flexible bronchoscopy. Patients were assigned in a 2:3 ratio for receipt of fospropofol 2 mg/kg (102 patients) or 6.5 mg/kg (150 patients) after fentanyl 50 mcg. Supplemental doses of fospropofol and fentanyl were permitted. The primary end point—sedation success as defined

in the previous studies—was achieved in 27.5% of patients in the 2 mg/kg group and 88.7% of patients in the 6.5 mg/kg group (*P* < 0.0001). Treatment success—defined as completion of the procedure without requiring alternative sedative or mechanical/manual ventilation—was achieved in 41.2%

of patients in the 2 mg/kg group and 91.3% in the 6.5 mg/kg group (*P* < 0.001). The mean number of supplemental fospropofol doses required for initiation and completion of the procedure was 2.9 in the 2 mg/kg group compared with 1.7 in the 6.5 mg/kg group (*P* < 0.001). The median time to seda-

tion was 18 minutes in the 2 mg/kg group and 4 minutes in the 6.5 mg/kg group. The median time to fully alert was 3 minutes in the 2 mg/kg group and 5.5 minutes in the 6.5 mg/kg group. Supplemental analgesics were used in 37.3% of patients in the 2 mg/kg group and in 16.7% of patients in the 6.5 mg/kg group ($P < 0.001$). The use of alternative sedatives was lower in the 6.5 mg/kg group (8% vs 58.8%; $P < 0.001$). Willingness to be treated again was 78.2% in the 2 mg/kg group and 94.6% in the 6.5 mg/kg group ($P < 0.001$). Absence of procedural recall was 55.4% in the 2 mg/kg group and 83.3% in the 6.5 mg/kg group ($P < 0.001$).^{15,16}

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

The product labeling lists no contraindications to the use of fospropofol.¹

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 the administration of fospropofol. Sedated patients should be continuously monitored, and facilities for maintaining 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.¹

Fospropofol may cause loss of spontaneous respiration. Apnea was reported in less than 1% of patients to whom fospropofol was administered using the standard or modi-

fied dosing regimens. Apnea was reported in 3% of patients who were given higher doses. Supplemental oxygen is recommended for all patients receiving fospropofol.¹

Fospropofol may cause hypoxemia detectable by pulse oximetry. Hypoxemia was reported in 4% of patients who were given the standard or modified dosing regimen. Hypoxemia was reported in 27% of patients who were prescribed higher doses. The risk of hypoxemia is reduced through the use of appropriate patient positioning and supplemental oxygen.¹

Fospropofol may inadvertently cause unresponsiveness or minimal responsiveness to vigorous tactile or painful stimulation in patients. Among patients sedated with fospropofol for colonoscopy, 4% became minimally responsive or unresponsive to vigorous tactile or painful stimulation. The duration of minimal responsiveness or complete unresponsiveness ranged from 2 to 16 minutes. Among patients sedated for bronchoscopy, the incidence was 16% and the duration ranged from 2 to 20 minutes.¹

Hypotension was reported in 4% of patients taking the standard or modified fospropofol dosing regimen and in 6% of patients taking higher doses. Patients with compromised myocardial function, reduced vascular tone, or reduced intravascular volume may be at increased risk for hypotension. A secure IV access catheter and supplemental volume replacement fluids should be readily available during the procedure.¹

Fospropofol does not prolong the QTc interval.¹⁷

Formate and phosphate are metabolites of fospropofol and may contribute to signs of toxicity following overdosage. Signs of formate toxicity are similar to those of methanol toxicity and are associat-

ed with anion gap metabolic acidosis.¹ Phosphate levels have been reportedly elevated following fospropofol administration; however, adverse reactions from increased serum phosphorus levels have not been reported.³ Exposure to large amounts of phosphate could cause hypocalcemia with paresthesia, muscle spasms, and seizures.¹

Caution is advised with the use of fospropofol in patients with hepatic function impairment. Dosage adjustments are not required in patients with mild to moderate renal function impairment; however, limited data are available for patients with CrCl of less than 30 mL/min.¹

A modified dosage regimen is recommended for patients 65 years of age and older. Hypoxemia was reported more frequently among patients 75 years of age and older than among patients 65 to 74 years of age.¹

The safety and effectiveness of fospropofol have not been evaluated in patients younger than 18 years of age. Use is not recommended in children.¹

Fospropofol is in pregnancy category B. Animal studies have not revealed impaired fertility or harm to the fetus caused by fospropofol. Fospropofol should be used in pregnancy only if clearly needed.¹ Use in labor and delivery is not recommended, including use in cesarean section deliveries. It is known that propofol crosses the placenta, and administration of fospropofol may be associated with neonatal respiratory and cardiovascular depression.¹

It is not known whether fospropofol is excreted in human milk; however, propofol is excreted in human milk. The effects of oral absorption of fospropofol and propofol are not known. Use is not recommended in mothers who are breast-feeding.¹

Table 4. Adverse Reactions With Fospropofol Occurring in 2% or More of Patients¹

<i>Adverse Reactions</i>	<i>Colonoscopy (n = 183)</i>	<i>Minor Procedures (n = 123)</i>	<i>Bronchoscopy (n = 149)</i>
Paresthesia	74%	63%	52%
Pruritus	16%	28%	16%
Hypoxemia	2%	1%	11%
Hypotension	2%	3%	7%
Nausea	0%	4%	1%
Vomiting	0%	3%	0%
Headache	1%	2%	1%
Procedural pain	0%	0%	2%

ADVERSE REACTIONS

Paresthesias have been commonly described after IV administration of fospropofol, occurring in up to 47% to 70% of patients taking fospropofol.^{4,8,10,14,15} Paresthesias (burning, stinging, or tingling sensations) generally occurred in the perianal and perineal regions and were usually described as mild to moderate in intensity, were transient and self-limited, generally occurred within 5 minutes after administration of the initial dose, and typically lasted 1 to 2 minutes.^{1,5,8,16,18} The pharmacologic basis for this effect is not known. Pretreatment with nonsteroidal anti-inflammatory agents, opioids, or lidocaine did not have any effect.¹

Other common adverse reactions have included pruritus, hypoxemia, and hypotension.^{4,8,10,14-16} Adverse reactions occurring in at least 2% of patients prescribed fospropofol are summarized in Table 4.

DRUG INTERACTIONS

Concomitant use of cardiorespiratory depressants, such as benzodiazepines and narcotic analgesics, with fospropofol may result in additive cardiorespiratory effects.¹

RECOMMENDED MONITORING

Continuously monitor pulse

oximetry, electrocardiogram, and frequent blood pressure measurements.¹

DOSING

Supplemental oxygen must be administered in all patients undergoing sedation with fospropofol.¹ Fospropofol is administered IV as a bolus injection. It should be administered through a secure, free-flowing peripheral IV line. The infusion line should be flushed with normal saline before and after administration of fospropofol.¹

The dose should be individualized and titrated to the level of sedation required for the procedure.¹ In clinical studies, fentanyl citrate 50 mcg was administered IV 5 minutes before the initial fospropofol dose.¹

The standard dose is an initial IV 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. The standard dose is recommended for patients 18 to 64 years of age who are healthy or who have mild systemic disease as categorized by the American Society of Anesthesiology (ASA P1 or P2). Adults who weigh more than 90 kg should be dosed as if they weigh 90 kg; adults who weigh less than 60

kg should be dosed as if they weigh 60 kg. Doses lower than those specified for the lower weight limit may be used to achieve lesser levels of sedation.¹

Patients 65 years of age and older and patients with severe systemic disease (ASA P3 or P4) should be administered 75% of the standard dose.¹

Supplemental doses should be administered only when patients can demonstrate purposeful movement in response to verbal or light tactile stimulation and no more frequently than every 4 minutes.¹

PRODUCT AVAILABILITY AND STORAGE

Fospropofol received approval from US Food and Drug Administration (FDA) in December 2008. It is available as a ready-to-use, injectable solution containing fospropofol 35 mg/mL (fospropofol disodium 1,050 mg in 30 mL) plus monothioglycerol and tromethamine. The 30 mL vials are intended for single-patient use only. Fospropofol should be drawn into sterile syringes immediately after the vials are opened; any unused portion should be discarded at the end of the procedure.¹ Fospropofol is not light sensitive. Filtering of the solution before use is not nec-

essary.¹ The pH of the solution is 8.2 to 9.¹² Fospropofol vials should be stored at controlled room temperature (25°C; 77°F), with excursions permitted between 15° and 30°C (59° and 86°F).¹

Fospropofol is compatible with dextrose 5% injection, dextrose 5% and sodium chloride 0.2% injection, dextrose 5% and sodium chloride 0.45% injection, sodium chloride 0.9% injection, Ringer's lactate injection, Ringer's lactate and dextrose 5% injection, sodium chloride 0.45% injection, and dextrose 5% and sodium chloride 0.45% with potassium chloride 20 mEq injection. Fospropofol should not be mixed with other drugs or fluids before administration. The drug is not physically compatible with midazolam or meperidine, and compatibility with other agents has not been assessed.¹

The FDA has recommended that fospropofol be classified as a controlled substance. A final scheduling decision will be made by the Drug Enforcement Administration.¹⁹

CONCLUSION

Fospropofol offers an alternative to midazolam for procedural sedation; however, classification as MAC limits use to those patients who otherwise may have required MAC sedation. For MAC sedation, fospropofol offers advantages over propofol, including lack of an emulsion formulation and lower peak concentrations, which improve tolerability.

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Continuing Education Case Study Quiz

Goal—The goal of this program is to educate pharmacists about the use of fospropofol for monitored anesthesia care sedation in patients undergoing diagnostic or therapeutic procedures.

Objectives—At the completion of this program, the pharmacist will be able to:

1. Describe the pharmacology and pharmacokinetics of fospropofol.
2. Discuss the risks associated with the use of fospropofol.
3. Discuss the potential benefit of fospropofol for an individual patient.
4. Apply information on the use of fospropofol to a case study.

Key Words—anesthetic agents, fospropofol, medical procedures, new drugs

1. Fospropofol is approved by the US Food and Drug Administration for use:

- A. as a surgical anesthetic.
- B. as continuous sedation in the intensive care unit setting.
- C. by a physician performing a diagnostic procedure.
- D. for monitored anesthesia care sedation in patients undergoing a procedure.

2. Fospropofol is:

- A. a lipid-soluble propofol prodrug.
- B. a propofol isomer.
- C. a water-soluble propofol prodrug.
- D. the active metabolite of propofol.

3. The breakdown products of fospropofol include:

- A. carbon dioxide and glucose.
- B. formaldehyde and phosphate.
- C. formic acid and sulfate.
- D. pyruvate and water.

4. The half-life of fospropofol is approximately:

- A. 6.5 minutes.
- B. 17 minutes.
- C. 46 minutes.
- D. 68 minutes.

Case History

MW is a 76-year-old woman scheduled to undergo bronchoscopy to evaluate a pneumonia that has failed to respond to multiple courses of antimicrobials. Her other medical conditions include osteoporosis, osteoarthritis, hypothyroidism, and depression. Her current medications include levofloxacin, risedronate, acetaminophen, levothyroxine, and escitalopram. MW is 5 feet 2 inches tall and weighs 110 pounds. Serum creatinine and electrolytes are within normal range. (*Answer questions 5 through 9 regarding MW's case.*)

5. The recommended dose of fospropofol for MW is:

- A. 244 mg.
- B. 293 mg.
- C. 325 mg.
- D. 390 mg.

6. Which of the following must be prescribed for MW in addition to the fospropofol?

- A. Meperidine
- B. Midazolam
- C. Prophylactic antibiotics
- D. Supplemental oxygen

7. During sedation, MW should be monitored with:

- A. electrocardiogram.
- B. frequent blood pressure determinations.
- C. pulse oximetry.
- D. All of the above

8. An additional dose of fospropofol is necessary before completion of the bronchoscopy. What is the recommended supplemental fospropofol dose for MW?

- A. 60 mg
- B. 72 mg
- C. 80 mg
- D. 96 mg

9. The second fospropofol dose only should be administered to MW if:

- A. it is within 4 minutes of the first dose.
- B. she is responsive to verbal or light tactile stimulation.
- C. she is unresponsive or minimally responsive to stimulation.
- D. she fully awakens before the procedure is complete.

10. Which of the following is the most common adverse effect associated with fospropofol?

- A. Hypotension
- B. Hypoxemia
- C. Paresthesias
- D. Pruritus

11. Which of the following is a potentially severe adverse effect associated with fospropofol?

- A. Apnea
- B. Hypotension
- C. Hypoxemia
- D. All of the above

12. A potential toxicity of one of the fospropofol breakdown products is:
- A. anion gap metabolic acidosis.
 - B. hyperchloremic metabolic acidosis.
 - C. metabolic alkalosis.
 - D. respiratory acidosis.
13. Which of the following administration steps is required with fospropofol?
- A. Dilution with 5% dextrose injection to a concentration of no less than 2 mg/mL
 - B. Filtration
 - C. Flushing the infusion line with normal saline before and after administration
 - D. Protection from light
14. Fospropofol is formulated as a:
- A. lipid emulsion.
 - B. powder for reconstitution.
 - C. solution.
 - D. suspension.
15. How should fospropofol be stored?
- A. At room temperature
 - B. At room temperature or in the refrigerator
 - C. In the refrigerator
 - D. In the freezer

Drug Evaluation: Fospropofol
 ACPE # 071-999-09-003-H01-P
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Activity Type: Knowledge based
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| 1. A B C D | 9. A B C D |
| 2. A B C D | 10. A B C D |
| 3. A B C D | 11. A B C D |
| 4. A B C D | 12. A B C D |
| 5. A B C D | 13. A B C D |
| 6. A B C D | 14. A B C D |
| 7. A B C D | 15. A B C D |
| 8. A B C D | |



The Washington State University College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.



PROGRAM EVALUATION

Please rate our continuing education offering by responding to the following questions.

1. How well were the learning objectives covered by this activity?

This program described the pharmacology and pharmacokinetics of fospropofol. Completely Fairly well Not at all

The program discussed the risks associated with the use of fospropofol. Completely Fairly well Not at all

After this program, I was able to discuss the potential benefit of fospropofol. Completely Fairly well Not at all

I was able to apply the knowledge from this educational program and other resources to answer questions associated with the case study. Completely Fairly well Not at all

2. The continuing education quiz questions required application of the information. Agree Disagree

3. The content of this article was relevant to the practice of pharmacy. Agree Disagree

4. My personal objectives in participating in this program were fulfilled. Agree Disagree

5. The program increased my knowledge of the subject area. Agree Disagree

6. I will be able to apply aspects of this program to my practice. Agree Disagree

7. The content of this article was scientifically sound. Agree Disagree

8. The article provided a balanced view of the product. Agree Disagree

9. The material was free of commercial bias. Agree Disagree

10. How long did it take you to complete this continuing education program? _____ hours

11. What other continuing education programs or topics would you like to see?
