# Pharmaceutical Approval Update

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## Fospropofol Disodium Injection (Lusedra)

**Manufacturer:** Eisai, Woodcliff Lake, N.J.

**Indication:** Fospropofol disodium, an intravenous (IV) sedative–hypnotic agent, is indicated for monitored anesthesia care sedation in adults undergoing diagnostic or therapeutic procedures.

**Drug Class:** Fospropofol disodium (dihydrogen{2,6-di-isopropylphenoxy}methyl phosphate) injection is a water-soluble prodrug of propofol. It is converted into propofol by alkaline phosphatase enzymes in the body after it is administered.

**Uniqueness of Drug:** Fospropofol is metabolized into propofol by the liver. After a bolus of fospropofol is given, blood levels of propofol reach peak levels that are lower than those of an equipotent dose of propofol, and the clinical effect is more sustained.

**Warnings and Precautions:**

***Monitoring.*** Only persons who are trained in administering general anesthesia and who are not involved in the diagnostic or therapeutic procedure should administer fospropofol. Facilities should be available to maintain a patent airway, provide artificial ventilation, administer supplemental oxygen, and begin cardiovascular resuscitation. Patients should be continuously monitored during sedation and throughout recovery for early signs of hypotension, apnea, airway obstruction, or oxygen desaturation.

***Respiratory depression.*** The product may cause a loss of spontaneous respiration. Apnea was reported in fewer than 1% of patients treated with fospropofol according to the standard or modified dosing regimen. When more than the recommended dose was given, apnea was reported in 3% of patients.

Supplemental oxygen is recommended for all patients receiving fospropofol. Dosages must be tailored for each patient and titrated to effect. Lower doses are required for patients 65 years of age or older or who have severe systemic disease. The additive cardiorespiratory effects of narcotic analgesics and sedative–hypnotic agents should be considered if they are given concomitantly with fospropofol. Patients should be assessed for their ability to demonstrate purposeful responses during sedation; patients who cannot respond may lose protective reflexes. Airway assistance maneuvers may be required to manage respiratory depression.

***Hypoxemia.*** Fospropofol may cause hypoxemia that is detectable by pulse oximetry. Hypoxemia was reported in 4% of patients receiving fospropofol according to the standard or modified dosing regimens. Hypoxemia was reported among patients who continued to respond purposefully to their health care provider after receiving the drug. Therefore, retaining responsiveness did not prevent patients from becoming hypoxemic after they received an injection. When a larger-than-recommended dose was given, hypoxemia was reported in 27% of patients. The risk of hypoxemia can be reduced by appropriate positioning of the patient and by the use of supplemental oxygen. Airway assistance maneuvers may be required to manage hypoxemia. The additive cardiorespiratory effects of narcotic analgesics and other sedative–hypnotic agents should be considered if they are given concomitantly with fospropofol.

***Patient unresponsiveness to stimulation.*** Fospropofol has not been studied for use in general anesthesia; however, it can inadvertently cause patients to become unresponsive or minimally responsive to vigorous tactile or painful stimulation. Four percent of patients who had been sedated for colonoscopy became minimally responsive or completely unresponsive to forceful tactile stimulation for 2 to 16 minutes. Among patients sedated for bronchoscopy, 16% became minimally or completely unresponsive to vigorous tactile or painful stimulation for 2 to 20 minutes.

***Hypotension.*** Hypotension has occurred after the use of fospropofol and has been reported in 4% of patients who were given the standard or modified dosing regimen. In patients receiving more than the recommended dose, hypotension was reported in 6% of patients. Patients with compromised myocardial function, reduced vascular tone, or decreased intravascular volume may be at an increased risk for hypotension. A secure IV access catheter and supplemental volume replacement fluids should be readily available. Additional pharmacological management may be necessary.

**Dosage and Administration.** Supplemental oxygen should be used for all patients undergoing sedation with fospropofol. Patients should be continuously monitored with pulse oximetry, electrocardiograms, and frequent blood pressure measurements.

***Standard regimen:*** The initial IV bolus dose is 6.5 mg/kg, followed by supplemental doses of 1.6 mg/kg as needed. The initial dose should not exceed 16.5 mL, and any supplemental dose should not exceed 4 mL.

***Modified regimen:*** A modified regimen (75% of the standard dose) is indicated for patients 65 years of age or older with severe systemic disease, based on the American Society of Anesthesiologists (ASA) physical status classification of P3 or P4. Supplemental doses should be given only when patients can demonstrate purposeful movements in response to verbal or light tactile stimulation and no more frequently than every four minutes. For adults weighing more than 90 kg, the dose should be the same as if they weighed 90 kg. For adults weighing less than 60 kg, the dose is the same as if they weighed 60 kg. The drug is intended for single-use administration only.

***Standard regimen for sedation.*** For adults between 18 and 65 years of age who are healthy or who have mild systemic disease (ASA P1 or P2), the standard dosing regimen of fospropofol is an initial IV bolus of 6.5 mg/kg, followed by sup-

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plemental doses of IV 1.6 mg/kg (25% of the initial dosage), as needed, to achieve the desired level of sedation. The dosage is limited by lower and upper weight bounds of 60 kg and 90 kg. Adults who weigh more than 90 kg are treated as if they weighed 90 kg. No initial dose should exceed 16.5 mL, and no supplemental dose should exceed 4 mL. Adults weighing less than 60 kg are treated as if they weighed 60 kg. Dosages lower than those specified for the lower weight limit may be used to achieve lower levels of sedation. In clinical studies, an opioid premedication (IV fentanyl citrate 50 mcg) was administered five minutes before the initial dose of fospropofol.

***Modified regimen for sedation in elderly patients or in those with severe systemic disease.*** Adults 65 years of age or older or those with ASA P3 or P4 status should receive initial and supplemental IV dosages of 75% of the standard dosing regimen. Fospropofol is administered as an IV bolus injection. In clinical studies, an opioid premedication (IV fentanyl citrate 50 mcg) was given five minutes before the first fospropofol dose.

**Commentary:** As an IV sedative–hypnotic agent in adults, fospropofol is a new water-soluble prodrug of propofol. The water-soluble formulation aims to bypass the disadvantages of propofol's lipid emulsion: pain on injection, risk of infection from decreased bacterial clearance, the need for a high lipid intake during long- term administration, and dose-related cardiac and respiratory depression.

Fospropofol be should be given by health care providers who are appropriately trained in administering general anesthesia. Patients should be continuously monitored during sedation and during recovery to check for early signs of hypotension, apnea, airway obstruction, or oxygen desaturation.

**Sources:** www.eisai.com; http://vam.anest.ufl.edu; www.news-medical.net/?id=44169

## Plerixafor (Mozobil)

**Manufacturer:** Genzyme Corporation, Cambridge, Mass.

**Indication:** Plerixafor, in combination with granulocyte–colony stimulating factor (G-CSF), is indicated for mobilizing hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).

**Drug Class:** The agent's chemical name is 1,1′-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane. The molecular formula is $C_{28}H_{54}N_8$, and the molecular weight is 502.79 g/mol.

**Uniqueness of Product:** Plerixafor, an inhibitor of the CXCR4 chemokine receptor, blocks binding of its cognate ligand, stromal cell–derived factor-1 (SDF-1). SDF-1 and CXCR4 play a role in the trafficking and homing of human HSCs to the marrow. After the stem cells are in the marrow, stem cell CXCR4 anchors these cells to the marrow matrix, either directly via SDF-1 or through the induction of other adhesion molecules. Plerixafor has resulted in leukocytosis and elevation of circulating hematopoietic progenitor cells in mice, dogs, and humans. CD34+ cells mobilized by plerixafor were capable of engraftment with long-term repopulating capacity up to one year in canine transplantation.

**Warnings and Precautions:**

***Tumor cell mobilization in leukemia.*** In mobilizing HSCs, plerixafor may cause movement of leukemic cells and subsequent contamination of the apheresis product (plerixafor). (The collection process is sometimes called leukapheresis or apheresis, the removal of white blood cells.) Therefore, plerixafor is not intended for HSC mobilization or harvest in patients with leukemia.

***Hematological effects:***

*Leukocytosis.* Administration of plerixafor with G-CSF increases circulating leukocytes as well as HSCs. White blood cell counts should be monitored in patients receiving plerixafor. Clinical judgment should be used if peripheral blood neutrophil counts exceed 50,000/mcL.

*Thrombocytopenia.* Thrombocytopenia has been observed in patients receiving plerixafor. Platelet counts should be monitored in all patients who receive plerixafor and who then undergo apheresis.

***Potential for tumor cell mobilization.*** When plerixafor is used with G-CSF for HSC mobilization, tumor cells may be released from the marrow and may collect in the leukapheresis product. The effect of potential re-infusion of tumor cells has not been thoroughly studied.

***Splenic enlargement and potential for rupture.*** Higher absolute and relative spleen weights associated with extramedullary hematopoiesis were observed following prolonged daily plerixafor subcutaneous (SQ) administration (two to four weeks) in rats at doses approximately four-fold higher than the recommended human dose based on body surface area. The effect of plerixafor on spleen size has not been evaluated. Patients who receive plerixafor with G-CSF and who report left upper-abdominal pain or scapular or shoulder pain should be assessed for splenic integrity.

***Pregnancy category D.*** Plerixafor may cause fetal harm when administered to pregnant women. It was teratogenic in animals. There are no adequate controlled studies of the drug during pregnancy. Women of childbearing age should be advised to avoid becoming pregnant while they are receiving plerixafor. If the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

**Dosage and Administration.** Plerixafor treatment is initiated after the patient has received G-CSF once daily for four days. The plerixafor dose is repeated for up to four consecutive days. The dose is based on 0.24 mg/kg of the patient's actual body weight and is given by SQ injection approximately 11 hours before apheresis begins. In patients with renal impairment (a creatinine clearance of 50 mL/minute or less), the dose should be decreased by one-third to 0.16 mg/kg. Each single-use vial is filled to deliver 1.2 mL of a 20-mg/mL solution containing 24 mg of plerixafor.

**Commentary:** Plerixafor, in combination with G-CSF, was designed to mobilize HSCs from the bone marrow into the bloodstream, where they could be collected, making it more likely for patients with certain types of cancers (NHL and MM) to undergo to autologous transplantation.

Currently, before transplantation takes place, patients usually receive a prescribed dose of chemotherapy, growth factors (G-CSF), or both, to help mobilize HSCs into the bloodstream.

These chemotherapeutic agents (cyclophosphamide with or without etoposide) may compromise an individual's immune system and can affect other organs of the body in a negative manner.

Following chemotherapy, the stem cells are released into the bloodstream and are collected in preparation for a transplant. For transplantation to take place, at least two million stem cells per kilogram of body weight must be collected. For many patients, this process can take three or four hours over multiple days to complete. Even then, some patients cannot achieve this number and a transplant is not possible. When patients actually undergo autologous transplantation, they first receive high-dose chemotherapy, radiation, or immunotherapy before they receive their own stem cells back.

Because high-dose chemotherapy has a more intense effect when it is associated with transplantation, more cells may be destroyed. In transplantation, one must take care with chemotherapy because of the possibility of total immunosuppression of the patient; too high a dose leaves patients vulnerable to secondary infections and transplant rejection. The status of the disease at the time of transplantation can affect outcome. For diffuse, large-cell lymphoma and follicular NHL, an autologous transplant in first remission may offer the best chance of long-term survival. Whether an autologous transplant is recommended at first remission depends on the type of lymphoma and the patient's risk factors. Therefore, the aim of plerixafor is to decrease the number of apheresis days; this causes less trauma for patients and also provides economic benefits for transplant centers. Plerixafor may also decrease the need for a second mobilization procedure because of failure to mobilize sufficient numbers of stem cells with G-CSF alone.

**Sources:** www.genzyme.com; www.helpwithcancer.org

## Fenofibric Acid Capsule, Delayed Release (TriLipix)

**Manufacturer:** Abbott Laboratories, Abbott Park, Ill.

**Indications:** Fenofibric acid is indicated as an adjunct to diet in combination with a statin to help reduce serum triglyceride and low-density lipoprotein-cholesterol (LDL-C) levels and to raise high-density lipoprotein-cholesterol (HDL-C) levels in patients with mixed dyslipidemia and coronary heart disease (CHD) or who have other forms of atherosclerosis (peripheral arterial disease, abdominal aortic aneurysm, or carotid artery disease); diabetes; or multiple risk factors that confer a 10-year risk for CHD greater than 20%.

***Severe hypertriglyceridemia.*** Improving glycemic control in diabetic patients showing fasting chylomicronemia usually obviates the need for pharmacological intervention. Markedly elevated levels of triglycerides (above 2,000 mg/dL) may increase the risk of pancreatitis. The effects of the new product in reducing this risk have not been adequately studied.

***Primary hyperlipidemia or mixed dyslipidemia.*** The capsule is indicated as adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, and apolipoprotein B levels and to increase HDL-C levels in patients with primary hyperlipidemia or mixed dyslipidemia.

***Limitations of use.*** No incremental benefits of the product on cardiovascular morbidity and mortality over and above that shown for statin monotherapy have been established.

***General considerations.*** In a large randomized, controlled trial that included patients with type-2 diabetes mellitus, fenofibrate at a dose equivalent to 135 mg of the capsule did not reduce CHD morbidity or mortality rates. Laboratory studies should be performed to establish that lipid levels are abnormal before TriLipix is prescribed.

**Drug Class:** This lipid-regulating agent is sold as a delayed-release oral capsule. Each capsule contains choline fenofibrate, equivalent to 45 mg or 135 mg of fenofibric acid. The chemical name of choline fenofibrate is ethanaminium,2-hydroxy-*N,N,N*-trimethyl,2-{4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate(1:1). The empirical formula is $C_{22}H_{28}C_lNO_5$, and the molecular weight is 421.91. Choline fenofibrate is freely soluble in water.

**Uniqueness of Drug:** The lipid-modifying effects of fenofibric acid have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor–α (PPAR-α). Fenofibric acid increases lipolysis and helps eliminate triglyceride-rich particles from plasma by activating lipoprotein lipase and by reducing production of Apo CIII, an inhibitor of lipoprotein lipase activity. The resulting decrease in triglycerides produces an alteration in the size and composition of LDL-C from small, dense particles (which are thought to be atherogenic) to large, buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPAR-α also induces an increase in the synthesis of HDL-C and Apo AI and AII.

**Warnings and Precautions:**

***Skeletal muscle.*** Fibrates and statin monotherapy increase the risk of myositis and myopathy and have been associated with rhabdomyolysis. The risk of rhabdomyolysis may be increased when fibrates are coadministered with a statin; a significantly higher rate of this complication is observed with gemfibrozil (Lopid, Pfizer). Prescribers should refer to the respective statin labeling for important drug–drug interactions that increase statin levels and that might increase the risk of rhabdomyolysis. The risk of serious muscle toxicity appears to be increased in elderly patients and in patients with diabetes, renal failure, or hypothyroidism.

Myalgia was reported in 3.3% of patients who were treated with TriLipix monotherapy, in 3.1% to 3.5% of patients receiving TriLipix plus statins, and in 4.7% to 6.1% of patients receiving statins alone.

Increases in creatine phosphokinase (CPK) to more than five times the upper limit of normal (ULN) did not occur with TriLipix monotherapy but did affect 0.2% to 1.2% of patients treated with TriLipix plus statins, compared with 0.4% to 1.3% of patients using statins alone.

Myopathy should be considered in all patients with diffuse myalgias, muscle tenderness or weakness, or markedly elevated CPK levels. Patients should promptly report unexplained muscle pain, tenderness, or weakness, particularly if they also have malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and TriLipix and statin therapy should be discontinued if elevated CPK levels occur or if myopathy or myositis is present.

***Serum creatinine.*** Reversible elevations in serum creatinine have been reported in patients receiving TriLipix as

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monotherapy or TriLipix with statins as well as in patients receiving fenofibric acid. Elevated creatinine levels were generally stable over time, with no evidence of continued elevations after long-term therapy. Levels tended to return to baseline values after treatment was discontinued. The clinical significance of these observations is not clear. Renal monitoring should be considered for patients with renal impairment after they take TriLipix and for patients at risk for renal insufficiency, such as the elderly and those with diabetes.

***Liver function.*** When administered at a dose of 135 mg once daily as monotherapy or when given with low-to-moderate doses of statins, the capsule has been associated with increases in serum aspartate transaminase (AST) and alanine transaminase (ALT) levels. However, after discontinuation of treatment or during continued treatment, transaminase values usually returned to normal. Increases in ALT and AST were not accompanied by increases in bilirubin or clinically significant increases in alkaline phosphatase.

Hepatocellular, chronic active, and cholestatic hepatitis, which have been noted with fenofibrate therapy, have been reported after exposures of weeks to several years. In rare cases, cirrhosis has been reported in association with chronic active hepatitis. Regular monitoring of liver function, including serum ALT, should be performed for the duration of therapy with TriLipix, and therapy should be discontinued if enzyme levels persist above three times the ULN.

***Cholelithiasis.*** Like fenofibrate (e.g., Tricor, Abbott), clofibrate (Atromid-S, Wyeth), and gemfibrozil (Lopid), TriLipix may increase cholesterol excretion into the bile, potentially leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. TriLipix therapy should be discontinued if gallstones are found.

***Concomitant oral anticoagulants.*** Caution should be exercised when TriLipix is given with oral anticoagulants, such as warfarin (Coumadin, Bristol-Myers Squibb). TriLipix may potentiate the anticoagulant effects of these agents, thereby prolonging the prothrombin time (PT) and the International Normalized Ratio (INR). Frequent monitoring of the PT and INR and dose adjustments of the oral anticoagulant are recommended until the PT and INR have stabilized in order to prevent bleeding complications.

***Pancreatitis.*** Pancreatitis has been reported in patients taking drugs of the fibrate class, including TriLipix. This event may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

***Hypersensitivity reactions.*** In rare cases, acute hypersensitivity reactions, including severe skin rashes requiring hospitalization and steroid treatment, have occurred during fenofibrate therapy, including rare spontaneous reports of Stevens–Johnson syndrome and toxic epidermal necrolysis.

***Hematological changes.*** Mild-to-moderate decreases in hemoglobin, hematocrit, and white blood cells have been observed in patients receiving initial TriLipix and fenofibrate therapy. Rare spontaneous cases of thrombocytopenia and agranulocytosis have been reported in association with fenofibrate.

***Mortality and coronary heart disease.*** The effect of TriLipix on CHD morbidity and mortality rates and on noncardiovascular mortality rates has not been established. Because of similarities between TriLipix and the other fibrates—fenofibrate, clofibrate, and gemfibrozil—the findings in several clinical studies with these fibrate drugs may also apply to this new medication.

*The FIELD Study.* The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was a five-year randomized, placebo-controlled study of 9,795 patients with type-2 diabetes mellitus treated with fenofibrate. Fenofibrate demonstrated a nonsignificant 11% relative reduction in the primary outcome of CHD events and a significant 11% reduction in the secondary outcome of total cardiovascular disease events. There was a nonsignificant 11% increase in total and coronary heart disease mortality, respectively, with fenofibrate compared with placebo.

*The Coronary Drug Project.* In a study of post–myocardial infarction patients treated for five years with clofibrate, there was no difference in mortality rates between clofibrate and placebo, but there was a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3% vs. 1.8%, respectively).

*The WHO Study.* In a study conducted by the World Health Organization (WHO), 5,000 subjects without known coronary artery disease received placebo or clofibrate for five years and were observed for an additional year. There was a statistically significant, higher age-adjusted all-cause mortality rate in the clofibrate group compared with the placebo group. Excess mortality was a result of a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

*The Helsinki Heart Study.* In a large study of 4,081 middle-aged men without a history of coronary artery disease, subjects received either placebo or gemfibrozil for five years, with a 3.5-year open extension afterward. More men in the gemfibrozil group died, but this figure did not achieve statistical significance. Although more cancer deaths occurred with gemfibrozil, cancers (except basal cell carcinoma) were diagnosed with equal frequency in both study groups. Even with the large number of subjects included in the study, statistical significance was not achieved, and the relative risk of death from any cause did not differ from that seen in the nine-year follow-up data from the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men who had been excluded from the primary prevention study because of known or suspected CHD. Subjects received gemfibrozil or placebo for five years. Although the number of cardiac deaths tended to be higher in the gemfibrozil group, this value was not statistically significant.

***Venothromboembolic disease.*** In the FIELD trial, pulmonary embolus (PE) and deep-vein thrombosis (DVT) were observed at higher rates with fenofibrate than with placebo. Of 9,795 patients enrolled in FIELD, 4,900 received placebo and 4,895 received fenofibrate. There were 48 DVT events (1%) in the placebo group and 67 (1%) in the fenofibrate group, and there were 32 PE events (0.7%) in the placebo group and 53

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(1%) in the fenofibrate group. In the Coronary Drug Project, more clofibrate patients experienced definite or suspected fatal or nonfatal PE or thrombophlebitis compared with the placebo group (5.2% vs. 3.3% at five years).

**Dosage and Administration:** TriLipix is available in strengths of 45 mg and 135 mg. Before receiving this medication, either alone or with a statin, patients should follow a lipid-lowering diet and should continue with this diet during treatment. The capsules can be taken without regard to meals. Serum lipids should be monitored periodically. The maximum dose is 135 mg once daily.

***Coadministration with statins for mixed dyslipidemia.*** TriLipix 135 mg may be coadministered with a statin in patients with mixed dyslipidemia. For convenience, the daily dose may be taken at the same time as a statin. Coadministration with the maximum dose of a statin has not been evaluated and should be avoided unless the benefits are expected to outweigh the risks.

***Severe hypertriglyceridemia.*** The initial dose of TriLipix is 45 to 135 mg once daily. The dosage should be tailored according to each patient's response and should be adjusted, if necessary, following repeated lipid determinations at four-week to eight-week intervals. The maximum dose is 135 mg once daily.

***Primary hyperlipidemia or mixed dyslipidemia.*** The TriLipix dose is 135 mg once daily.

***Impaired renal function.*** TriLipix should be initiated at a dose of 45 mg once daily in patients with mild-to-moderate renal impairment. The dose should be increased only after an evaluation of the effects on renal function and lipid levels at this dose. TriLipix should be avoided in patients with severely impaired renal function.

***Elderly patients.*** The dose depends on the patient's renal function.

**Commentary:** TriLipix, a delayed-release capsule, can be used along with diet to help lower triglyceride and LDL-C levels and to raise HDL-C levels. This drug is the first fibrate to be approved for use in combination with a statin. The active component in TriLipix is the same as in TriCor, an older formulation of Abbott's fenofibric acid. The newer formulation comprises fenofibric acid, a binder, and optional excipients.

In clinical studies of almost 2,700 patients with mixed dyslipidemia, TriLipix was more effective in controlling the three lipids when used with a statin compared with the use of the statin alone. TriLipix has not been shown to prevent heart disease or heart attacks. It is not indicated for patients with liver, gallbladder, or severe kidney disease; nursing mothers; or those allergic to any ingredient in the product.

**Source:** www.rxabbott.com ■