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Ms. Teresa Watkins
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Comments to the Anesthetic and Life Support Drugs Advisory Committee for the May 7, 2008 meeting to discuss the new drug application (NDA) 22-244, fospropofol disodium injection (35 mg/mL) (proposed tradename Aquavan), MGI Pharma, Inc., for the proposed indication of sedation in adult patients undergoing diagnostic or therapeutic procedures.

Dear Ms. Watkins:

On behalf of the American Society of Anesthesiologists (ASA), and its over 42,000 physician members, who believe that patient safety is paramount, we thank you for the opportunity to provide comments to the Anesthetic and Life Support Drugs Advisory Committee during its review of the new drug application (NDA) 22-244, fospropofol disodium injection (35 mg/ml) (proposed tradename Aquavan) (hereinafter "fospropofol"), MGI Pharma, Inc., for the proposed indication of sedation in adult patients undergoing diagnostic or therapeutic procedures. For the many patient safety reasons outlined in the comments that follow, we respectfully request that the labeling for fospropofol include a bolded statement, similar to the label for propofol, that reads:

"For general anesthesia or monitored anesthesia care (MAC) sedation, fospropofol disodium injection (35 mg/ml), AQUAVAN should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. Patients should be continuously monitored, and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available."

By way of background, ASA, founded in 1905, is the national educational, research and scientific association of physicians organized to raise and maintain the standards of the medical practice of anesthesiology and improve the care of the patient. For over 30 years, the ASA has documented significant advances in patient safety and has received unparalleled recognition for its efforts. In 2005, the ASA submitted comments to the FDA opposing a petition submitted by the American College of Gastroenterologists (ACG) that sought the removal of warning

language from the package insert for propofol (Diprivan®) (Docket Number 2005P-0267; Comments Opposing Citizen Petition Requesting Change in Propofol Labeling). Citing significant patient safety concerns, the ASA argued that the so-called “anesthesia training warning” that was present in the initial labeling for propofol remained valid and should remain as part of the product labeling. Because of the similarities between propofol and fospropofol, including the potential for adverse events, we believe that both products should bear similar warnings.

Propofol is a powerful anesthetic agent with all of the risks of general anesthesia and it is widely understood that fospropofol, a water soluble prodrug that is rapidly hydrolyzed in patients, derives its sedative and anesthetic actions by releasing propofol into the blood and tissue. The major concern about the use of propofol is the risk that patients, whose responses to propofol are often unpredictable, may enter a state of deep anesthesia or general anesthesia, even if only moderate sedation was intended. Under general anesthesia, patients may face a number of life-threatening complications including airway occlusion, apnea, hypoxia and cardiovascular collapse. Individuals not trained and experienced in the administration of general anesthesia may not be able to restore breathing or normal cardiac activity in time to prevent a catastrophe. In addition there are no reversal agents available for either propofol or fospropofol should too much be given. Therefore, since fospropofol is converted to propofol in the bloodstream and tissues, and the risks associated with propofol remain the same, the labeling for fospropofol should include the same labeling requirement as detailed above: that the drug be administered only by individuals trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure.

1. Pharmacokinetics of Fospropofol

Fospropofol is a water soluble prodrug that is rapidly hydrolyzed by alkaline phosphatase which is present in the blood, but mainly resides in tissues. Fospropofol confers some advantages over current formulations of the highly hydrophobic propofol which are prepared in lipid emulsions. These lipid-based formulations cause pain in the veins into which they are injected, present stability and contamination issues, and may result in a significant lipid load to patients receiving the drug. In addition, intravenous administration of fospropofol, like the similar prodrug fosphenytoin (used as an anticonvulsant), is somewhat simplified as the rate of increase of the plasma concentrations of the active compounds (propofol and phenytoin) depends more on the hydrolysis of the prodrug to the active form than on the rate of injection of the prodrug. For these reasons fospropofol deserves appropriate consideration for NDA approval.

However, unlike fosphenytoin, it is not clear whether the delayed systemic appearance of propofol from the hydrolysis of fospropofol conveys any safety advantages sufficient to allow personnel untrained in anesthesia to administer fospropofol. Furthermore, the delayed release of the active form may actually complicate titration of plasma levels of propofol to the desired effect in the continuum of sedation and anesthesia, and produce an increased potential for dose stacking. In addition high interindividual variability in the rate and the fractional conversion of fospropofol into propofol increases the potential for unexpected serum propofol levels for any individual patient.

Unlike the hydrolysis of fosphenytoin where there is a nearly 1:1 molecular release of phenytoin to the circulation from fosphenytoin, both of the detailed pharmacokinetic studies of fospropofol in humans have shown that the fraction appearing in plasma (or bioavailability, F) is less than unity ($F \cong 0.65$) and that the apparent bioavailability shows a nonlinear relationship to dose.^{1,2} The decreased bioavailability of propofol from its parent fospropofol is further substantiated by the discrepancy between the molar ratio of the two drugs (1.86) and the ‘dose equivalency’ (approximately 6.0 as opposed to 1.86 on a molecule-for-molecule basis). Furthermore, the proportion of fospropofol converted to propofol is nonlinearly related to dose. Gibiansky et al.³ showed that not accounting for the nonlinearity of this hydrolytic process led to an overestimation of the C_{\max} of propofol at low doses and underestimation at high doses of approximately 43% and 36%, respectively (i.e. a nearly 2-fold greater propofol C_{\max} would occur at high fospropofol doses predicted from the kinetics at low fospropofol doses). The tight, carefully controlled dosing protocols presented by MGI Pharma for this NDA may have resulted in minimizing interindividual variability in propofol release, but higher or off label dosing that could occur in an uncontrolled clinical setting, would be expected to produce disproportionately large anesthetic effects. Such conditions strongly argue for the presence of personnel sufficiently educated and trained to deal with the full continuum of sedation and anesthesia.

Dutta and Ebling⁴ first described the pharmacokinetic and pharmacodynamic differences of lipid-free and lipid-bound propofol in studies performed in rats. They found that lipid-free propofol differed in potency and had a larger volume of distribution. Human studies on fospropofol indicate that the resulting propofol behaves in a similar fashion to the lipid-free formulation studied in a rat model. The EC_{50} for EEG median frequency depression was 30% lower for fospropofol-derived propofol than for propofol from the lipid emulsion.^{1,2} These data do not suggest that fospropofol has pharmacokinetic or pharmacodynamic disadvantages, but do suggest that it is not appropriate to make direct comparisons of plasma concentration data between studies in which fospropofol was administered against those in which a lipid emulsion was administered. Instead, the propofol concentrations resulting from fospropofol may require adjustment by a factor of approximately 1.5 and patients may be further along the continuum of sedation and anesthesia than would be expected from plasma propofol concentration data alone.

Part of the ‘unpredictability’ of propofol derives from its steep concentration-response relationship. That is, small changes in plasma propofol concentration can produce large changes in effect. The Hill coefficient, which is used to quantify ‘steepness’ is variously reported between 1.6 and 5 (quite steep to very steep, respectively) for propofol depending on which drug effect is being analyzed.^{1,5} In contrast, midazolam has a less steep concentration response relationship with Hill coefficients in the 0.75 to 1.0 range.⁶ This makes fospropofol dose titration a more painstaking process and it makes it more unpredictable in the sense that a small dose may produce a minimal effect, but a repeated small dose may suddenly produce a profound anesthetic effect.

The sedation protocols constructed by MGI Pharma seem to be cognizant of both the variable ‘bioavailability’ of fospropofol and the steep propofol concentration-response curve in that the initial dose is fairly conservative (6.5 mg/kg) and is followed by appropriately spaced (no sooner than 4 minutes) repeat doses set at one quarter of the initial dose up to a total of 3 repeat doses.

However, this regimen, while it produced few complications or adverse events in colonoscopy clinics, resulted in a high sedation ‘failure’ rate of nearly 20% and an unacceptably high incidence of deep sedation/general anesthesia when these failures were ‘rescued’ with midazolam. The high rate of complications when midazolam is added to an opioid-propofol regimen should not be surprising as work by Vinik et al.⁷ has shown that the ‘sedation synergy’ index is increased from 1.3 for opioid-propofol to 2.5 when midazolam is added.

Practitioners facing, or in the midst of, a painful procedure when a sedation failure occurs in a patient being dosed by a careful and conservative fospropofol dosing regimen will be left with four choices: (1) abandon the procedure, (2) press on with the procedure without further sedative drugs, (3) administer additional fospropofol, risking the unpredictability of the steep concentration-response curve and production of deep sedation or anesthesia or (4) adding another sedative/hypnotic/analgesic drug, such as a benzodiazepine or a narcotic which also is likely to lead to deep sedation or anesthesia. Options (1) and (2), while safe, are obviously bad choices for the patient. Options (3) and (4) could be safely entertained only if a trained anesthesia provider were caring for the patient. None of these options are good for the patient but the complications that might occur with the increase of fospropofol doses or the addition of other drugs could be avoided if personnel educated and trained in the practice of anesthesia were present to properly manage the increased depth of sedation that would likely be brought about through the addition of other sedative, hypnotic, or analgesic medications.

2. Patient Safety Requires Extensive Training to Use Propofol and thus Fospropofol

Propofol, whether administered in a lipid emulsion formulation or as fospropofol, is a powerful anesthetic agent that can produce unpredictable levels of sedation along the continuum from sedation to general anesthesia. It is efficacious and safe when administered by practitioners with the appropriate training and appropriate monitoring technology. Because sedation is a continuum (see Table 1. of Attachment 1) and the propofol plasma (or effect site) concentration-response relationship is steep, it is not always possible to predict how an individual patient will respond. Delayed time to peak effect can increase the difficulty of titrating a drug with a steep response curve and a narrow margin of safety. Patients differ in their individual reactions to a standard dose. Beside the known approximately 20-fold variation in the rate of metabolism of propofol, there appears to be additional variability in the production of propofol from fospropofol and nonlinear conversion as larger cumulative doses are administered.

There are no antagonist or reversal medications for propofol and thus fospropofol. This is an important factor that distinguishes propofol and fospropofol from other sedatives, such as benzodiazepines and narcotics, currently used by non-anesthesiologist physicians. Due to the potential for rapid, profound changes in sedative/anesthetic depth and the lack of antagonist medications, agents such as propofol and fospropofol require special attention. Even if moderate sedation is intended, patients receiving propofol or fospropofol should receive care consistent with that required for deep sedation. This means that the clinician administering propofol or fospropofol must be competent to recognize a state of deep sedation or general anesthesia and be able rescue a patient experiencing any of the complications associated with the deeper level of sedation or general anesthesia.

General anesthesia frequently entails the loss of the ability to maintain ventilatory function, and patients often need assistance in maintaining a patent airway. Positive airway pressure may be required because of depressed spontaneous ventilation or drug-induced dependence of neuromuscular function. A patient under general anesthesia is at risk for life-threatening respiratory and cardiovascular changes, including hypoxia, hypoventilation, bradycardia, tachycardia, hypotension and hypertension.

Because patients may readily enter a state of general anesthesia, even if a lower level of sedation was planned, The Joint Commission (TJC) requires that clinicians intending to administer deep sedation be qualified to rescue patients from general anesthesia and be competent to manage an unstable cardiovascular system as well as a compromised airway and inadequate oxygenation and ventilation. The joint ASA/ AANA statement on propofol use indicates that, “personnel who administer propofol should be qualified to rescue patients whose level of sedation becomes deeper than initially intended and who enter, if briefly, a state of general anesthesia.”⁸

To be qualified to rescue patients from general anesthesia, the physician responsible for the use of propofol should have the education and training to manage the potential medical complications of sedation and anesthesia. “The physician should be proficient in airway management, have advanced life support skills appropriate for the patient population, and understand the pharmacology of the drugs used.”⁸ The physician should be proficient in recognizing the sometimes subtle signs of adverse respiratory or cardiac events and should have the knowledge and technical skills (e.g. rapid intubation) to manage cardiovascular events and compromised airways.

It is possible for non-anesthesiologist physicians to have the requisite training and experience to manage deep sedation. Privileges to administer general anesthesia awarded by the facility in which a physician practices would be the best indicator of adequate training. Omission of a warning label from the fospropofol package insert may encourage the use of fospropofol by practitioners with inadequate training and experience in non-accredited facilities where credentialing is not required, such as private offices. We note that a large percentage of procedures are now being performed in private offices, and the proportion is expected to grow.

In 1999, the Institute of Medicine (IOM) identified ASA as the sole exception to its observation that “few professional societies or groups have demonstrated a visible commitment to reducing errors in health care and improving patient safety.”⁹ As an organization long committed to improving the quality and safety of patient care, ASA is very concerned with the adequacy of some of the anesthesia and sedation training offered to other medical specialties. For example, we have serious questions about the level and sophistication of such training when a relatively recent brochure from a symposium, sponsored principally by the American College of Gastroenterology, on “Endoscopic Sedation: Preparing for the Future,” listed a section on “Maximizing Patient Safety” that dedicated just 20 minutes to a lecture entitled “Airway Management for Dummies.”

Gastroenterologists are concerned with “the troublesome and increasing problem of undertrained endoscopists,” attributed to the propensity of hospitals to replace subspecialty-trained endoscopists with less costly generalists.¹⁰ If undertrained endoscopists lack proficiency in endoscopy, it is difficult to imagine that they have the requisite education and experience in the medical specialty of anesthesiology.

3. Patient Safety Requires the Right Staffing and the Right Facility

A. The right staffing

The current labeling for propofol includes the precaution that the individual who administers the drug should “not [be] involved in the conduct of the surgical/diagnostic procedure.” This reflects the well-established principle that there must be an independent practitioner whose sole responsibility is administering propofol and monitoring the patient to assess level of consciousness and to identify early signs of hypotension, bradycardia, apnea, airway obstruction and/or oxygen desaturation.^{8, 11} The corollary benefit to patient safety, of course, is that a practitioner conducting a surgical/diagnostic procedure during which propofol is administered is free to devote his full attention to the procedure, secure in the knowledge that an expert in anesthesia is devoting his/her full attention to monitoring the patient’s response to the drug. Logic and the clinical pharmacology of fospropofol dictate that similar language should be on the label of fospropofol.

The July 2003 issue of Outpatient Surgery magazine reported 74.8% of respondents in an on-line reader survey felt that propofol administration by RNs was a patient-safety risk and 71.2% believed administering anesthesia with propofol to be outside of an RN’s scope of practice.^{8, 11} According to the article, many RNs are uncomfortable using propofol, feeling that unpredictable and instantaneous patient reactions such as loss of an airway render administration and monitoring of the drug beyond their competence. In a 2002 ruling on a petition filed by registered nurses, the Florida Board of Nursing declared the administration of propofol to be beyond the scope of practice of an RN, even if an anesthesiologist were supervising. The challenges to nurses administering anesthesia with propofol include the greater risk of respiratory or cardiovascular complications presented by growing number of obese or other patients, as well as the multitasking expected of RNs but not of anesthesiologists or CRNAs whose only responsibility is to the patient, as discussed in an editorial in the August 2005 issue of the same magazine calling upon the FDA to reject the 2005 ACG petition.

The American Association for the Accreditation of Ambulatory Surgical Facilities (AAAASF), the largest accrediting body for office based surgery facilities in the country, has explicitly taken the position that propofol, unlike other intravenous sedation, may not be administered by a registered nurse and the ASA feels that same standard should apply to fospropofol.

B. The right facility

The warning label on propofol contains a sentence, stating that “Patients should be continuously monitored, and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.” Again, the ASA believes that similar recommendations pertain for fospropofol.

Organizations that accredit hospitals, such as TJC,¹² and ambulatory surgical facilities, such as TJC, the Accreditation Association for Ambulatory Health Care (AAAHC) and the American Association for the Accreditation of Ambulatory Surgical Facilities (AAAASF), require the immediate availability of a staff expert in airway management and advanced cardiopulmonary resuscitation, as well as immediate access to emergency equipment.

It is unlikely that every office-based endoscopy suite is properly staffed and equipped for deep sedation and general anesthesia. Currently, only 23 states regulate office-based surgical facilities through regulation, statute or guidelines. Of those 23 states, only 11 require regulation of office-based surgical facilities. 27 states do not regulate such facilities at all. Again, from a patient safety standpoint, the critical needs include, having 1) the personnel on hand who can ensure continuous monitoring and proper care, including emergency care, of a patient under general anesthesia, and 2) the appropriate tools and equipment to do so.

Not including a package insert warning for fospropofol would remove inhibitions on the administration of fospropofol, not just in hospitals and ambulatory surgery centers and on the physicians credentialed to perform deep sedation by those facilities, but also on physicians with minimal anesthesia training working in under-staffed and under-equipped offices that might be quite remote from the nearest emergency medical care.

4. Conclusion

As we have shown, propofol is a powerful sedative hypnotic, capable of producing general anesthesia along a continuum with a steep drug concentration-response relationship which accounts for the current labeling warning requiring its administration by a trained anesthesia provider. Published research studies on the clinical pharmacology of fospropofol show that its sedative and anesthetic actions are due to the production, by hydrolysis, of propofol. Furthermore, the clinical pharmacology of fospropofol presents several additional concerns such as variability in metabolism, significantly differing interpatient effects, and dangerous synergies with other medications that necessitates a similar warning as propofol.

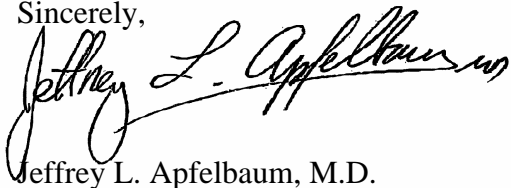
Studies indicate that the conversion of fospropofol to propofol is variable and nonlinearly related to the dose, and that the peak effect is delayed, thereby making the required titration more difficult. In addition, there are very real dangers of provider misuse based on the prolonged time to effect and the extended period before a sedation failure is recognized or declared. This concern is compounded by the lack of a reversal agent, should oversedation occur.

In summary, the ASA remains concerned about the significant dangers to patients of inadequately trained individuals who may choose to use fospropofol “off label,” either combined with other drugs or, by repeated dosing given too quickly. Either of these situations would have the risks compounded if fospropofol was administered to patients with significant pathophysiologic compromise or comorbidities. In all of these situations, there is a high likelihood that the sedation “continuum” could advance from moderate sedation to deep sedation or general anesthesia much faster than an inadequately trained individual could manage, thus putting the patient at significant risk.

Given these important patient safety concerns along with the concerns expressed during our presentation the ASA encourages the FDA to include a substantially similar warning label on fospropofol (Aquavan) as currently required for propofol. As leaders in patient safety, the ASA strongly believes that such a label requirement will help ensure the safety of patients undergoing diagnostic or therapeutic procedures who receive fospropofol for sedation.

Thank you for your consideration.

Sincerely,

A handwritten signature in black ink that reads "Jeffrey L. Apfelbaum, M.D." The signature is written in a cursive style with a long horizontal line extending from the end.

Jeffrey L. Apfelbaum, M.D.
President
American Society of Anesthesiologists

Attachments:

1. ASA Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists
2. ASA Statement on Safe Use of Propofol

References:

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