

Robert Impastato MD
Director of Anesthesia HVEC-NAPA
Fishkill NY 12524

4/20/08

FDA
Center for Drug Evaluation and Research

Dear Anesthetic and Life Support Drugs
Advisory Committee,

I am contacting you at this time to comment on the new drug application for (NDA) 22-44, fospropofol disodium injection (35mg/ml) (proposed trade name Aquavan), MGI Pharma, Inc.

Before discussing my concerns with the proposed drug and its indications I would like to introduce myself. Prior to becoming a physician I was a pharmacist. While being an Anesthesiologist for the past 18 years, I have been an active participant in VBMC's P&T committee, Medication Use committee, and have served as their chairperson. In addition I have been a longstanding member of the hospitals quality and practice improvement committees. For the past five years I have been the Director of Anesthesia at Hudson Valley Endoscopy Center and the Mobile Coordinator for NAPA in the Hudson Valley. I have actively participated in, supervised and coordinated over 40,000 IV endoscopic sedation cases during that time.

In addition I have participated in numerous GI sedation cases on the hospital level, including EUS's and ERCP's.

As a concerned clinician and scientist I have reviewed numerous articles related to fospropofol and have become alarmed for the following reasons.

1. Although the water- soluble preparation of fospropofol at low doses bypasses the minor disadvantages of the lipid formulation, patient variability is a significant factor. The prodrug preparation has a delayed time to peak concentration of propofol... A drug that has a slower onset of action as compared to the drug that it is metabolized to (propofol) has increased patient variability. It is very difficult to determine if a lack of desired response is due delayed onset or increased requirements. If a physician administers a second dose before the initial dose takes peak effect, catastrophic respiratory depression could occur. This is then compounded by the fact that it has a longer duration the propofol, which requires the administration by someone trained in the administration of general anesthesia. If this occurs, would you rather have an anesthesiologist present, or gastroenterologist who has an endoscope in his hands?
2. The drug is being touted as "propofol lite" in controlled trials at specific dosages. These trials were designed for political and economic reasons to avoid the FDA's own restriction on propofol, which this drug is metabolized to. If a prodrug like this, with a more complex five compartmental model of metabolism is released into the mainstream without dose, administration control and restraints, extreme adverse events will surely occur. At higher doses the initial trials were stopped by the initial manufacturer, Guilford Pharmaceuticals for a reason.
3. We have been fooled numerous times before by drugs in trials before they were released into the general population and their gene pools. Need I mention Raplon, I personally had a patient that was nearly impossible to ventilate after its administration. A controlled trial with specific endpoints is not the whole story.
4. I am also concerned with the prodrug's side effect of paresthesias. When the fospropofol is metabolized into propofol phosphate and formaldehyde by alkaline phosphates, when get into patient variability once again, and what will happen when the drug gets into the general population. Whether it is the formaldehyde or its metabolite formate that causes the paresthesias, this does not occur with propofol.