AstraZeneca

March 26, 2001

Dear Health Care Provider,

I am writing to inform you that based on a recent review of new clinical trial data, the Food and Drug Administration (FDA) has determined that there may be important safety concerns when propofol, marketed by AstraZeneca as DIPRIVAN® (propofol) Injectable Emulsion, is used for sedation in the Intensive Care Unit (ICU) in pediatric patients. I would like to remind you that propofol is not approved in the US for sedation in pediatric ICU patients and should not be used for this purpose.

The FDA s determination was made based on the review of data from a randomized, controlled, clinical trial that evaluated the safety and effectiveness of DIPRIVAN versus standard sedative agents (SSA) in pediatric ICU patients. In that study a total of 327 pediatric patients were randomized to receive either DIPRIVAN 2% (113 patients), DIPRIVAN 1% (109 patients), or an SSA (eg, lorazepam, chloral hydrate, fentanyl, ketamine, morphine, or phenobarbital). DIPRIVAN therapy was initiated at an infusion rate of 5.5 mg/kg/hr and titrated as needed to maintain sedation at a standardized level. The results of the study showed an increase in the number of deaths in patients treated with DIPRIVAN as compared to SSAs. A total of 25 patients died during the trial or within the 28-day follow-up period: 12 (11%) in the DIPRIVAN 2% treatment group, 9 (8%) in the DIPRIVAN 1% treatment group, and 4 (4%) in the SSA treatment group. In the opinion of FDA, careful review of the deaths failed to reveal a correlation with underlying disease status, nor did the review reveal a definite pattern to the causes of death. In order to better understand this potential safety issue AstraZeneca will initiate a new clinical trial designed specifically to evaluate any differences in adverse events and deaths in pediatric patients randomized to propofol or SSAs for ICU sedation.

We would like to reemphasize that propofol is currently not approved for sedation in pediatric ICU patients in the US and should not be used for this purpose. It is important that you forward any adverse event information involving propofol to AstraZeneca (for DIPRIVAN) at the Information Center 1-800-236-9933, 8 am - 7 pm or to the FDA via the MedWatch system. Copies of the MedWatch form are available on the FDA web site *(http://www.fda.gov/medwatch/index.html* or *http://www.fda.gov/medwatch/safety.htm)* as listed.

If you would like additional information related to the trial, please call the AstraZeneca Information Center.

Sincerely,

David Goodale, DDS, PhD
Medical Leader for Pain, Anesthesia and Infection Products
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Enclosure

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