

For Industry

FDA Public Health Advisory: Subject: Reports of Blue Discoloration and Death in Patients Receiving Enteral Feedings Tinted With The Dye, FD&C Blue No. 1

September 29, 2003

Dear Health Care Professional:

The Food and Drug Administration (FDA) would like you to be aware of several reports of toxicity, including death, temporally associated with the use of FD&C Blue No. 1 (Blue 1) in enteral feeding solutions. In these reports, Blue 1 was intended to help in the detection and/or monitoring of pulmonary aspiration in patients being fed by an enteral feeding tube. Reported episodes were manifested by blue discoloration of the skin, urine, feces, or serum and some were associated with serious complications such as refractory hypotension, metabolic acidosis and death. Case reports indicate that seriously ill patients, particularly those with a likely increase in gut permeability (e.g., patients with sepsis), may be at greater risk for these complications. Because these events were reported voluntarily from a population of unknown size, it is not possible to establish the incidence of these episodes.

A causal relationship between systemic absorption of Blue 1 and the reported serious and life-threatening patient outcomes (including death) has not been definitively established. Indeed, it would be very difficult to establish a clear, causal relationship in the setting of complex medical issues often seen in patients receiving feedings via enteral tubes. However, *in vitro* evidence that Blue 1 can be a mitochondrial toxin lends plausibility to the idea that Blue 1 could cause these kinds of serious adverse effects if significant or persistent serum levels of the dye were to occur. From the reports, it appears that neither the concentration nor the total amount of Blue 1 used in the enteral feeding solutions was unusually high compared to other patients in whom no toxicity was observed. Thus, if there is a causal relationship between the dye and the serious outcomes, there could be underlying patient-related factor(s) that allow significant absorption of Blue 1 in some enterally fed patients.

While we are not able at this time to establish a cause-and-effect relationship between the reported serious and life-threatening patient outcomes and the use of the dye, nonetheless, given the seriousness of the potential complications, we believe health care professionals should be notified of these reports.

As background, FD&C Blue No. 1 is a water-soluble dye allowed by the FDA for use in foods, drugs and cosmetics, based on numerous studies in animals. Data from life-exposure animal studies supports an ADI (acceptable daily intake) of Blue 1 of 12.0 milligrams/kilogram body weight/day. The dye is batch certified by the FDA and is widely used in food products (candies, confections, beverages, etc.) in amounts consistent with good manufacturing practices (generally at parts per million). There have been no reports of toxicity associated with this general use. Toxicity has been reported only in association with Blue 1 tinting of enteral feedings, intended as a means of visually detecting pulmonary aspiration. This use, although a common practice for nearly 30 years, has never been evaluated by the FDA for safety or utility (i.e., there has been no evaluation by the FDA of the sensitivity and specificity of its use in this manner).

SUMMARY OF REPORTS

- As of September, 2003, the FDA is aware of 20 cases from the scientific literature or in FDA post-marketing adverse event reports associating the use of blue dye in tube feedings with blue discoloration of body fluids and skin, as well as more serious complications. There have been 12 reported deaths and one case with an unknown outcome.
- In more than 75% of all reported cases, patients had a reported history of sepsis (and therefore likely altered gut permeability) before or during systemic absorption of Blue 1.
- Time of onset of toxicity from first use of Blue 1 varied from several hours to 20 days of continuous use in enteral feedings.

At this time, the FDA believes practitioners should be aware of the following points:

- Use of Blue 1-tinted enteral feedings for detecting aspiration has been associated with several serious adverse events, including death, although a direct causal relationship has not been definitely established.
- The safety of Blue 1-tinted enteral feedings for detecting aspiration has not been documented.
- Based on the reports received to date, patients at risk for increased intestinal permeability, which includes those with sepsis, burns, trauma, shock, surgical interventions, renal failure, celiac sprue, or inflammatory bowel disease, appear to be at increased risk of absorbing Blue 1 from tinted enteral feedings.
- In addition to the possibility of systemic toxicity, Blue 1-tinted enteral feedings may interfere with diagnostic stool examinations, such as the hemocult test.
- Other blue dyes, such as methylene blue and FD&C Blue No. 2, may have similar if not greater toxicity potential than Blue 1 and would not be

appropriate replacements.

The FDA will continue to closely monitor reports for additional events. We encourage all health professionals to report any serious adverse events occurring with Blue 1-tinted enteral feedings to the FDA's MedWatch program at 1-800-FDA-1088 tel, 1-800-FDA-0178 fax, or online at <http://www.fda.gov/medwatch/>. Additional information on color additives, in general, may be accessed at <http://www.cfsan.fda.gov/~dms/col-toc.html>

Sincerely yours,

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