Miller, Diane M. (CDC/NIOSH/EID)

From: droman@rdg.boehringer-ingelheim.com
Sent: Thursday, September 20, 2007 2:49 PM
To: NIOSH Docket Office (CDC)
Cc: VBaker@cle.boehringer-ingelheim.com
Subject: Ben Venue Laboratories Comments on NIOSH Docket Number 105
Importance: High
Attachments: NIOSH Docket Number 105 Ben Venue Laboratories Comment 9.20.07.pdf

Dear Ms. Miller:

Attached please find comments on NIOSH Docket Number 105 from Ben Venue Laboratories. If you have any questions, please do not hesitate to contact me at (203) 228-0287 or my colleague Valerie Baker at (440) 201-3457.

Best regards, Donna
Donna Lyn Roman
Director, Government Affairs & Public Policy
Boehringer Ingelheim Pharmaceuticals, Inc.
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Ben Venue Laboratories, Inc.,

SUBMITTED VIA MAILAND E-MAIL to niocindocket@cdc.gov

September 20, 2007

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Re: Ben Venue Laboratories Comments on DHHS (NIOSH) Publication No 2004-165 [NIOSH Docket Number 105]

Dear Ms. Miller:

Ben Venue Laboratories (BVL) welcomes the opportunity to comment on the public documents noted above that are under review by the National Institute for Occupational Safety and Health (NIOSH) and its peer-review panel of experts. We request that you remove amiodarone and valporate sulfate from the Hazardous Drug Alert and have provided scientific risk-based explanations supporting our request below. We have also included some general comments on the Drug Alert and the process for updating it for your consideration.

BVL, a wholly owned subsidiary of Boehringer-Ingelheim in Bedford, Ohio, is the leading contract manufacturer of sterile injectables and parenteral pharmaceutical products for the U.S. pharmaceutical industry. It also markets its own line of generic injectables to hospitals and alternate care markets through its Bedford Laboratories (BLI) division. BLI's product lines include oncology, cardiovascular, anesthesia, antipsychotic and more. BVL, which employs more than 1,100 people, has been under contract with the National Cancer Institute (NCI) since 1967 to develop parenteral dosage forms for many anticancer agents. It has also manufactured various AIDS-specific drugs in conjunction with the NCI.

Request Amiodarone De-listing from the NIOSH Hazardous Drug Alert

NIOSH has designated amiodarone (also referred to as Cordarone®) for inclusion on its list of new FDA drugs that fit the NIOSH Hazardous Drug Alert criteria. NIOSH based the listing decision on the Product Insert. Specifically, NIOSH has designated cancer, Pregnancy Category D, reproductive toxicity,

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and organ toxicity as the bases for listing amiodarone. Amiodarone is not genotoxic. BVL believes that amiodarone does not warrant listing in the NIOSH alert. A scientific risk-based explanation is provided below.

BVL formulates amiodarone for intravenous use. Amiodarone is supplied at a concentration of 50 mg/mL in 3 mL single-use vials, 9 and 18 mL multiple-use vials. The active drug substance, amiodarone, is an antiarrhythmic drug with predominant class III effects of lengthening cardiac action potential and blocking myocardial potassium channels leading to slowed conduction and prolonged cardiac refractoriness. However, amiodarone also possesses electrophysiologic characteristics including blocking sodium channels, is sympathomimetic and has negative inotropic effect. Amiodarone is intended for use only in patients with indicated life-threatening arrhythmias because it is accompanied by substantial toxicity. Amiodarone is indicated for the treatment and prophylaxis of life-threatening ventricular arrhythmias.

The NIOSH designations (as specified above including cancer, Pregnancy Category D, reproductive toxicity, and organ toxicity) are documented in the amiodarone Package Insert. However, the Package Insert also established the doses used clinically. Intravenous administration (first 24 hours) includes 150 mg (first 10 minutes), 360 mg (next 6 hours) and 540 mg (over the remaining 18 hours). Maintenance intravenous therapy is 720 mg per 24 hours. The intravenous doses of amiodarone to achieve pharmacologic efficacy are indeed quite high. As such, amiodarone is not close to being considered to be a potent drug based on accepted standard and therefore should not be listed as hazardous. It is critical to recognize that potency is a function of dose and not a function of the degree or severity of side effects or toxicity achieved at very high doses.

The hazard profile in human and/or animal studies provides only a partial explanation for potential human health risks to health care providers. It is also important to consider exposure. In the absence of exposure, there is no adverse human health risk. Amiodarone is supplied as a 50 mg/mL solution in single or multiple use vials. Handling of these dosage forms does not require reconstitution and should not result in exposure to the patient or the health-care provider (e.g., pharmacist or nurse). Thus, there is negligible exposure and hence, essentially no risk to health-care providers from handling of amiodarone. In the highly unlikely event of skin contact with amiodarone, there is no evidence to suggest that this drug will be absorbed across the skin. In addition, the drug is in solution and is not volatile precluding inhalation exposure.

In conclusion, amiodarone does not meet the Hazardous Drug Alert criteria as established by NIOSH, and use and/or handling of amiodarone does not constitute a human health risk to health care providers. We appreciate your consideration of our request to remove amiodarone from the Hazardous Drug Alert.

Request Valproate Sodium De-listing from the NIOSH Hazardous Drug Alert

NIOSH has designated valproate sodium (also referred to as Depacone®) for inclusion on its list of new FDA drugs that fit the NIOSH Hazardous Drug Alert criteria. NIOSH based the listing

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decision on the Package Insert. Specifically, NIOSH has designated cancer, Pregnancy Category D, reproductive toxicity, and organ toxicity as the bases for listing valproate sodium. Valproate sodium is not genotoxic. BVL believes that valproate sodium does not warrant listing in the NIOSH alert. A scientific risk-based explanation for our request is provided below.

BVL formulates valproate sodium for intravenous use. The same drug in slightly different forms (acid and disodium salt) is also formulated for oral administration (valproic acid and divalproex). Valproate sodium is supplied at a concentration of 100 mg/mL in 5 mL single-use vials. The active drug substance, valproate sodium, is an anti-seizure drug. The mechanism by which valproate controls seizures has not been established although involvement with the neurotransmitter GABA has been postulated. Valproate sodium is intended for use only in patients with certain types of seizures as monotherapy or adjunctive therapy. The intravenous form of the drug is used when patients cannot take the oral forms.

The NIOSH designations (as specified above including cancer, Pregnancy Category D, reproductive toxicity, and organ toxicity) are documented in the valproate sodium Package Insert. However, the Package Insert also established the doses used clinically. Valproate sodium is administered at an initial dose of 10 mg/kg/day. The intravenous and oral dose levels are similar. The initial dose is escalated depending on clinical need by 5-to-10 mg/kg/week. Ordinarily, optimum clinical therapy is achieved at doses below 60 mg/kg/day. For a 50 kg person, the initial dose is 500 mg/day. For a 50 kg person, the escalated dose can reach 3000 mg/day. The intravenous doses of valproate sodium to achieve pharmacologic efficacy are extraordinarily high. As such, valproate is not considered to be a potent drug at the doses administered. It is critical to recognize that potency is a function of dose and not a function of the degree or severity of side effects or toxicity achieved at very high doses.

The hazard profile in human and/or animal studies provides only a partial explanation for potential human health risks to health care providers. It is also important to consider exposure. In the absence of exposure, there is no adverse human health risk. Valproate sodium is supplied as a 100 mg/mL solution in single-use vials. Handling of these dosage forms does not require reconstitution and should not result in exposure to the patient or the health-care provider (e.g., pharmacist or nurse). Thus, there is negligible exposure and hence, essentially no risk to health-care providers from handling of valproate sodium. In the highly unlikely event of skin contact with valproate sodium, there is no evidence to suggest that this drug will be absorbed across the skin. In addition, the drug is in solution and is not volatile precluding inhalation exposure.

In conclusion, valproate sodium does not meet the Hazardous Drug Alert criteria as established by NIOSH. Use and/or handling of valproate sodium does not constitute a human health risk to health care providers. We appreciate your consideration of our request to remove valporate sodium from the Hazardous Drug Alert.

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General Comments

The utility of the NIOSH Hazardous Drug Alert will be lost if the list covers drugs which do not carry a significant and practical occupational risk, and we therefore encourage NIOSH to carefully re-evaluate the list. We believe that it is critical for NIOSH to consider dose-response and bioavailability of a drug as well as mechanisms of action in its hazard assessment process, and also to incorporate weight-of-evidence considerations.

A clear and transparent peer-review system for adding/deleting or updating information on drugs approved by FDA on a periodic basis (e.g., quarterly) is essential to ensure the effectiveness of the NIOSH Hazardous Drug Alert. In order to reduce any unnecessary risk to healthcare professionals/employees, we suggest development of a publicly available repository for this information, preferably available via a web-based link through which the healthcare community can easily access the most up-to-date information. We also strongly encourage NIOSH to share the criteria used to select the NIOSH Alert Committee/Panel of Experts to demonstrate its balanced representation of the healthcare community and support the credibility of its process. In addition to these comments, BVL is aware of and supports the comments submitted by PhRMA and strongly encourages NIOSH to adopt their recommendations.

Conclusion

Thank you for this opportunity to comment on the Hazardous Drug Alert. As always, we are pleased to work with NIOSH to protect the safety of the healthcare community. If you have any questions on our comments or recommendations, please feel free to contact me at (440) 201-3457.

Sincerely,

Valerie M. Baker, CSP, CHMM
Environmental Health and Safety Manager