



P.O. Box 8299, Philadelphia, PA 19101-8299

Division of American Home Products Corporation

Philip J. de Vane, M.D.  
Vice President, Medical Affairs  
and North American Medical Director

March 21, 2001

Dear Health Care Professional:

Wyeth-Ayerst Pharmaceuticals would like to make you aware of two recent changes to the Cordarone® I.V. (amiodarone HCl) prescribing information. The safety and efficacy of amiodarone I.V. in the pediatric population have not been established; therefore, its use in pediatric patients is not recommended. Nevertheless, Wyeth-Ayerst Pharmaceuticals is aware that Cordarone® I.V. (amiodarone HCl) is used off-label to treat arrhythmias in pediatric patients.

The first addition to the text is in the **DOSAGE AND ADMINISTRATION** section of the label. Text was added that states, "Cordarone I.V. has been found to leach out plasticizers, such as DEHP [di-(2-ethylhexyl)phthalate] from intravenous tubing (including PVC tubing). The degree of leaching increases when infusing Cordarone I.V. at higher concentrations and lower flow rates than provided in **DOSAGE AND ADMINISTRATION**." DEHP is used in various plastic medical devices, generally to increase flexibility.

An expert panel recently concluded that, based on data from animal studies, there was concern that exposure to DEHP may adversely affect male reproductive tract development during fetal, infant, and toddler stages of development if the exposure in these immature stages is several fold higher than in adults, a situation that might be associated with intensive medical procedures such as those used in critically ill infants.<sup>1</sup> Although a no-observable-adverse-effect level (NOAEL) by the oral route was identified for sexually mature rats (3.7–14 mg/kg per day), a NOAEL was not identified for rats in the postnatal stage. The maximum anticipated exposure to DEHP following Cordarone I.V. administration under conditions of pediatric administration was calculated to be about 1.9 mg/kg per day for a 3-kg infant, which produces a safety margin of between about twofold and sevenfold.

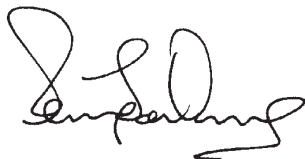
If use of the product in pediatric patients is believed to be medically warranted, in order to reduce the potential exposure of these patients to plasticizers, alternative methods of dosing and administration (e.g., bolus dosing in 1-mg/kg aliquots as described by Perry et al<sup>2</sup>) may be considered.

The second addition relates to the **PRECAUTIONS, Pediatric Use** section of the label. Text has been added that describes a "gasping syndrome" in neonates, which may be fatal, following the administration of intravenous solutions containing the preservative benzyl alcohol. The text states, "Cordarone I.V. contains the preservative benzyl alcohol. There have been reports of fatal 'gasping syndrome' in neonates (children less than 1 month of age) following the administration of intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse."

Serious adverse events or product problems should be reported to the FDA via the MEDWATCH Program by telephone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, via the MEDWATCH website at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or by mail (using postage-paid form) to MEDWATCH, The FDA Medical Products Reporting Program, Food & Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787.

A copy of the full prescribing information is enclosed for your reference. Please contact Wyeth-Ayerst Medical Affairs at 1-800-934-5556 if you have further questions.

Sincerely,

A handwritten signature in black ink, appearing to read "Philip J. de Vane". The signature is fluid and cursive, with a large initial "P" and "J".

Philip J. de Vane, M.D.

<sup>1</sup> NTP-CERHR Expert Panel Report on di(2-ethylhexyl) phthalate. *National Toxicology Program*. US Department of Health and Human Services, October 2000.

<sup>2</sup> Perry J, Fenrich A, Hulse J, et al. Pediatric use of amiodarone: efficacy and safety in critically ill patients from a multicenter protocol. *J Am Coll Cardiol*. 1996;27:1246–1250.