



## FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

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### MEMORANDUM

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DATE: October 24, 2003

TO: Chair, Members and Invited Guests

FROM: Bob A. Rappaport, M.D.  
Director  
Division of Anesthetic, Critical Care and Addiction Drug Products  
Office of Drug Evaluation II, CDER, FDA

RE: Overview of the November 18, 2003 meeting of the Anesthetic and Life Support Drugs Advisory Committee to discuss the risk of QT prolongation and Torsades de Pointes associated with droperidol

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In March 2001, Janssen Pharmaceutica Products, L.P. discontinued marketing of droperidol internationally, except in the United States, due to serious concerns regarding the drug's potential to cause life-threatening ventricular dysrhythmias. After receiving an internal analysis by Janssen, and performing our own internal review of our postmarketing safety database for droperidol and a thorough review of the literature, the Agency placed a boxed warning on droperidol labels in November of 2001. This boxed warning has generated controversy in the anesthesia community. This controversy has led the Agency to continue to explore the most beneficial way to reconcile the significant potential for cardiotoxicity associated with droperidol with the known, widespread use of the product in the perioperative and conscious sedation setting.

While droperidol is commonly used below the doses labeled for the prevention of perioperative nausea and vomiting, the serious cardiovascular adverse events reported in association with droperidol have included cases observed following exposure to these lower doses. Rather than withdrawal, the Agency adopted a more measured approach of warning prescribing health care workers through a boxed warning. The boxed warning has been used by the Agency for other drugs posing similar adverse cardiovascular risk. The Agency is compelled to use warnings in labeling to describe "...serious adverse

reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association, . . . *a causal relationship need not be established.* [emphasis added] . . . Special problems, particularly those that may lead to death or serious injury, may be required . . . to be placed in a prominently displayed box.<sup>1</sup>” The evidence for droperidol having a potential to cause a deleterious effect on cardiac repolarization which could predispose to the occurrence of Torsades de Pointes and sudden death is quite strong, even if causality has not been fully established.

In addition, the Agency committed to conducting a pharmacokinetic/pharmacodynamic study to evaluate the dose-related effects of droperidol on the QTc interval. That study was performed at The University of Indiana. Although it was prematurely terminated due to significant neuropsychiatric adverse events and therefore was inconclusive, the data were not reassuring. Significant outliers for delayed repolarization following droperidol dosing were detected at doses as low as 2.5 mg, the lowest labeled dose.

Since the results of that study became available, the Agency has been exploring the options for obtaining data that would satisfy the regulatory standards for the demonstration of safety and efficacy at doses lower than those currently labeled and data that would clearly define the risks associated with use of the product in general. However, after extensive internal discussion, we have been unable to agree on any practical study design that would inform a thorough risk-benefit analysis for the perioperative setting and that would be reassuring if negative, given the data available to date. The studies that would be most likely to provide this data would, by design, require extensive capital, both human and financial.

We have chosen to convene a session of the Anesthetics and Life Support Drugs Advisory Committee at this time in order to seek your assistance in determining the most appropriate way for the Agency to proceed in dealing with this significant public health concern in light of the available data. In addition to gaining advice on the most appropriate plan for evaluating this complex issue, it is equally important to gain advice on how the Agency might best communicate the risks of the cardiovascular toxicity associated with droperidol to the medical community.

We have provided this background package in order to assist you in this discussion. It includes documents that review or document the Agency’s prior decisions and actions related to droperidol cardiotoxicity, federal regulations related to the use of “Boxed Warnings” and other warning information used in drug labeling, and a White Paper defining the Agency’s current policy on the risk management of drugs associated with QT prolongation and Torsades de Pointes. It also provides published literature reports describing the potential for cardiotoxicity related to droperidol, as well as articles reviewing key concepts in drug-related cardiotoxicity.

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<sup>1</sup> Title 21 Code of Federal Regulations, part 201.57

We greatly appreciate your participation in this discussion and look forward to seeing you in November.