

Pediatric Advisory Subcommittee Meeting
Open Meeting
February 3 & 4, 2004

Overview

CDER's Division of Medical Imaging and Radiopharmaceutical Drug Products reviews and regulates imaging drugs that are administered in vivo and are used for diagnosis or monitoring of disease with a variety of different modalities, such as radiography, computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI) and radionuclide imaging. We are meeting to seek your advice on the role that imaging drugs play in the diagnosis and management of cardiac disease in the pediatric population. Specifically we are seeking advice on the types of imaging drugs being used routinely in the pediatric population and the purpose of that use. We are also interested in discussing the safety profile of these drugs and the potential clinical benefits of their use. This information will help the Division understand where there is a critical need for further cardiac imaging drug development for the pediatric population. This information will help us prepare and issue relevant written requests for pediatric studies.

To prepare you for these deliberations, you will hear a series of expert presentations on the use of cardiac imaging drugs in the pediatric population. These presentations will be focused on the four main imaging modalities: MRI, CT, ultrasound and nuclear imaging. The drug classes to be discussed include gadolinium, iodinated contrast, microspheres and radiopharmaceuticals.

This briefing book provides additional background material including several recent review articles and the Draft Guidance for Industry; Developing Medical Imaging Drug and Biologic Products (Parts 1-3). The draft guidance reflects the Agency's current thinking on the development of imaging drugs and biological products. The draft guidance discusses such issues as safety, clinical indications and trial design.

Also included in this briefing book are labels for each of the drugs to be discussed by Dr. Solomon Iyasu, Medical Team Leader with the Division of Pediatric Drug Development, on the morning of February 3. Per section 17 of the Best Pharmaceuticals for Children Act, Dr. Iyasu will report on adverse events for the following drugs that were granted market exclusivity under 505A of the Federal Food, Drug, and Cosmetic Act: Paxil (paroxetine), Celexa (citalopram), Pravachol (pravastatin) and Navelbine (vinorelbine). We have included the labels for each of these drugs in your background package so you can review them prior to the meeting.

Introduction

To date the Division has not issued a written request for pediatric studies for any imaging drugs with cardiac applications that are approved for use in adults. Of those approved, the iodinated contrast agents are the only drug class that has labeling for use in the

pediatric population for cardiac imaging. Many of these drugs are approved for conventional angiography and are labeled for use starting at the age of 1 year. Other cardiac imaging drugs that are routinely used in adults and sometimes in children do not have pediatric labeling.

Traditionally adult cardiac imaging drug approvals have been based on data from studies performed in a population suffering from coronary atherosclerotic disease. This disease process is not noted to be prominent in the pediatric population and therefore, extrapolation of the adult efficacy data to the pediatric population has not been considered a viable option. To date, we have received waiver requests for pediatric studies which cited lack of use in a substantial number of pediatric patients and the lack of the occurrence of atherosclerotic coronary artery disease in this population.

Many of the products that are approved in adults detect or measure such parameters as myocardial ischemia, left ventricular opacification, and endocardial border delineation which intuitively should have potential use in the pediatric population. Therefore finding the appropriate pediatric populations in which this type of data would have clinical benefit is one of the goals of this discussion.

Since many of these products are not labeled for pediatric use, we have limited safety information for this population. Any information that we have stems from voluntary reports of adverse events to FDA's Adverse Event Reporting System (AERS). A search of this database was performed for each drug class. One or two of the more widely used marketed products per drug class were used for purposes of the search. There were no reports noted for specific drugs in the radiopharmaceutical and microsphere drug classes. There were, however, several reports noted by drug for the gadolinium and iodinated drug classes. Most of these were reports of nausea and vomiting and of allergic type reactions for the gadolinium drug class and allergic type reactions (one of which resulted in death) for the iodinated drug class. This database does not allow for sorting based on the purpose of the study, therefore trends in use could not be identified as part of this search. It is important to note that several gadolinium products and iodinated products are approved for use in the pediatric population for CNS imaging.

The agenda for the Pediatric Advisory Subcommittee meeting begins the morning of February 3 and will include presentations on each imaging modality on that afternoon. The meeting will conclude with deliberation on a series of questions to be held on February 4, 2004. The questions for deliberation are provided in draft form below.

Draft Questions for February 3 & 4, 2004

1. Given the differences in cardiac disease processes that occur in adults and children, in what cases (if any) can adult data from approved imaging drugs be extrapolated to pediatric patients in whom cardiac imaging is needed? If so, in what cardiac disease states?

2. Assuming further studies in pediatric patients are needed, we would like you to further define the gaps in our knowledge regarding imaging agents to be evaluated for cardiac imaging applications.

Please discuss each of the following questions for each imaging modality (cardiac CT, cardiac MRI, cardiac US, and cardiac nuclear imaging)

- a) What imaging agents need further study?
 - b) What populations should be studied?
 - c) What disease states should be studied?
 - d) What endpoints should be used?
 - e) How should a trial be designed?
 - f) How should the standard for comparison be defined? Is there a gold-standard?
3. Are there new developments in the field of adult cardiac imaging that may have potential application to the pediatric population? Can we anticipate the need for future drug development for pediatric cardiac imaging?