Radiopharmaceutical Drugs Advisory Committee Meeting

FDA Approves Three Imaging Agents and Considers Two Other Agents and the Gastric Emptying Petition

With its traditional end of the year flourish, during December, the Food and Drug Administration (FDA) approved three medical imaging agents — a cardiac imaging agent, a renal and brain imaging agent, and a radiocontrast agent. The agency is also reviewing two technetium-99m (^{99m}Tc)-labeled cardiac imaging agents, and a petition to expand the package labeling of ^{99m}Tc sulphur colloid to include gastric motility, in the wake of its Radiopharmaceutical Drugs Advisory Committee (RDAC) Meeting held in November. The FDA also outlined its stance on positron emission tomography (PET) drugs during the RDAC meeting.

On December 29, the FDA approved two nuclear imaging agents, CardioGen-82® — a rubidium-82 generator used in myocardial perfusion imaging with PET, which is marketed by Squibb Diagnostics, a division of Bristol Myers-Squibb, and TechneScan DTPA® —a technetium-99m-labeled brain and renal imaging agent, marketed by Merck, Sharp and Dohme Research Laboratories. On December 7, the Agency approved Berlex Laboratories Inc.'s radiocontrast agent, Osmovist® for intrathecal administration.

Robert West, assistant to the group leader for medical imaging at the FDA, told *Newsline* that the Agency would not render a final decision on new drug applications (NDA) for two cardiac imaging agents discussed during the RDAC meeting — teboroxime (CardioTec® Squibb) and technetium sestamibi (Cardiolite® E. I. Du Pont De Nemours and Company, Inc.) until early Spring. "While they're clinically approvable," he said, "there are other deficiencies in the applications needing resolution prior to approval." He said the FDA was working with the two companies to resolve those areas.

Teboroxime NDA

In the CardioTec® NDA, Squibb is seeking approval to use CardioTec® as a myocardial perfusion agent "as an adjunct in the evaluation of coronary blood flow at rest and stress." More specifically, the company is seeking to use the drug to distinguish normal from abnormal myocardium in patients with suspected coronary artery disease. The advisory committee supported such an indication for the drug, as did the FDA staff reviewer at a presentation during the RDAC Meeting.

Teboroxime is a boronic acid derivative of ^{99m}Tc dioxime that is one of a class of neutral lipophilic ^{99m}Tc-labeled compounds, which concentrate in the myocardium and other organs, such as the lungs and the liver. The radiopharmaceutical would be made available in a sterile, nonpyrogenic lipophilic kit containing 2 mg of the active ingredient. This formulation would be reconstituted in 1 ml of ^{99m}Tc up to a maximum of 100 milliCuries. The solution must then be heated at 100 degrees Celsius for 15 minutes, cooled, and then given by intravenous injection.

In the company's presentation before the RDAC, Jason Zielonka, MD, Squibb's director of worldwide clinical research, pointed out that teboroxime "has pharmacologic properties that are well-suited to clinical imaging of the myocardium. . . .the distribution is linear, with flow. . .there is high myocardial extraction, there is rapid blood clearance, and there is a short myocardial residence time. . . .[which] permits the option of reimaging a patient within a very short period of time." He also listed other characteristics of the agent that make it clinically advantageous, such as its being ^{99m}Tc-labeled in-house and therefore readily available.

Using overall clinical impression as the gold standard, in phase II trials, researchers at eight centers analyzed 155 patients who underwent imaging with teboroxime as well as either or both of two other procedures — thallium examinations and cardiac catheterization. Dr. Zielonka told the committee that teboroxime exhibited a sensitivity of about 82% and a specificity of about 93%, relative to overall clinical impression. In addition, he called these values "very useful clinically" and said that "they compare very nicely with values that are generally in the literature for thallium."

In the FDA's presentation of their studies on the drug, Lionel Lieberman, MD, PhD, pointed out that the agent has a "technetium label with photopeak energies well-suited to gamma camera work, lower radiation exposures per milliCurie of dose [than

thallium] and the availability of the material in a kit form that can be used in emergencies. Because of its rapid washout from the myocardium, it is possible to do a rest cardiac study and follow it in a few hours with the stress part of the study." For these reasons, he concluded, ". . .CardioTec® is safe and can be used to identify abnormal myocardial tissue, realizing that its main strength lies in its sensitivity, rather than specificity. That is, perhaps, where we would want the strength of a study that is going to be used for a screening test."

Technetium Sestamibi NDA

Du Pont sought a somewhat narrower indication in the NDA for Cardiolite® The diagnostic applications that Du Pont sought were myocardial perfusion imaging for the diagnosis and localization of myocardial infarction in coronary artery disease and ventriculography using the first-pass technique. The RDAC recommended approval of the requested labeling. The FDA reviewer, Elias Chacalos, MD, said that FDA staff would recommend approval with a revision in the package insert. "Technetium sestamibi has been shown to be a myocardial imaging agent, which, when used with other diagnostic modalities, can detect myocardial infarction and localize it broadly [even] in inferior or inferior-posterior myocardial wall," he concluded.

Outlining the clinical benefits of technetium sestamibi, James Smith, PhD, director of research and development for the imaging agents division of Du Pont, said Cardiolite® has demonstrated prolonged myocardial retention, low lung activity, and moderate liver activity, which decreased over time. "The combination of the prolonged myocardial retention and the decreasing liver activity allows the images to become superior with time. So the longer one waits, the better the quality of the images, essentially." He noted that Cardiolite® also will be marketed in a kit formulation with a long shelf-life, that is easy to prepare and "consistently gives very high radiochemical yields" and that the compound is stable after it is reconstituted.

Presenting a review of the company's clinical trials of the agent, Norman LaFrance, MD, Du Pont's director of diagnostics/medical research, said data from 186 subjects in two well-controlled studies examining the efficacy of the agent in the diagnosis of myocardial infarction indicated that the sensitivity ranges from 83% to 95% and the specificity from 78% to 100%, for doses of 10 to 30 milliCuries.

Charles Boucher, MD, associate professor of medicine, Harvard Medical School, associate physician, Massachusetts General Hospital, one of the Cardiolite® investigators, presented his experience with the drug before the RDAC. He emphasized that "Cardiolite® in my experience, is able to simultaneously, with a single study, measure both myocardial perfusion and ventricular function, and so is unique compared to all other techniques. In the assessment of myocardial infarction, determination of the extent of the perfusion abnormality and the degree of the decrement in myocardial or ventricular function are very powerful measures of the size of the infarct and the determinant of patient prognosis."

Dr. Boucher also noted that "because of the prolonged retention in the myocardium, and the ability to uncouple the stress or the rest injection from the actual image acquisition, you have time to acquire the studies. This does improve efficiency and flexibility. . . .It allows acute therapeutic monitoring. . . . .Because this agent can be injected and imaged later after the patient is stabilized, [it] can be injected before the thrombolytic therapy is given, the images can be obtained, and then a follow-up study can be [performed] after the thrombolytic therapy has a chance to work in the acute setting."

In presenting the FDA's review of Cardiolite® Dr. Chacalos noted the potential advantages of technetium sestamibi — the ability to measure ventricular ejection fraction and image the myocardium with one dose, "sharper and less granular" images than those obtained with thallium, and less redistribution than thallium.

Increased Flexibility with ^{99m}Tc

Captain William H. Briner (USPHS, ret.), director of the radiopharmacy and nuclear medicine laboratory, associate professor of radiology, Duke University Medical Center, and a consultant to the RDAC, told *Newsline* that he was "hopeful and favorably impressed by FDA's review of the drugs." He added that "each drug is a good one, they are worthwhile and needed."

(continued on page 19A)

since both agents are ^{99m}Tc-based, "they are readily available in the hospital and provide a little more flexibility than thallium."

(continued from page 14A)

Alun G. Jones, PhD, associate professor of radiology, Harvard University Medical School, who has worked with both agents, although primarily with technetium sestamibi, told *Newsline* that since both agents are ^{99m}Tc-based, "they are readily available in the hospital and provide a little more flexibility than thallium."

He said these agents will "most likely. . . find an initial niche where thallium can't be used" as in situations where the need for the test cannot be forseen, such as in the emergency room.

He also described how technetium sestamibi could be particularly useful under such circumstances because it remains stable in the patient for a number of hours, enabling injection and then subsequent imaging after the patient is stabilized.

Gastric Emptying Petition

After once again reviewing the long-standing gastric emptying petition — which seeks approval of the oral administration of ^{99m}Tc sulphur colloid mixed with food to image and quantify gastric emptying — the FDA staff has resubmitted the petition, recommending that the Agency approve a broadened indication of upper gastrointestinal motility in the package insert for ^{99m}Tc sulphur colloid.

A. Eric Jones, MD, of the FDA staff, told RDAC members, however, "that the literature reviewed under this petition underscores the need to develop a specific test meal and perform the evaluation with defined method. There is great variability in results from institution to institution, but intrainstitutional variability appears to be minimal once uniform methodology is practiced. For the data obtained from this procedure to be clinically useful, each institution must develop its own normal range of results."

The FDA presented its current stance on the regulation of PET radiopharmaceuticals during the RDAC meeting. Acting Chairman of the RDAC, John Keyes, MD, director, division of nuclear medicine and professor of radiology, Georgetown University Hospital, read a statement outlining an agreement that the Agency and industry had reached on the regulation of PET drugs, which included the following points: Due to the favorable safety profile of most PET radiopharmaceuticals, the FDA can properly apply new-drug regulatory requirements and still observe its responsibility to public health; initial NDAs for PET drugs that have been clinically useful will establish a pattern for subsequent applications, allowing the use of both retrospective and prospective data; current good-manufacturing-practice regulations will be applied to the production of PET drugs through guidelines to be established; and "until NDAs for PET drugs are approved, existing and near-term future PET facilities can operate under the current regulatory environment."

In response to concerns raised by some of the RDAC members about how PET centers would be expected to operate in such a regulatory environment, John Palmer, MD, acting director of the FDA's division of medical imaging, surgical, and dental drug products, said, "The hope would be that even though FDA does not intend at this time to exert regulatory authority over PET centers that are not under a new drug application, the mechanism that is set up will make it so that operating under an approved new-drug application would be the most appropriate and logical step. . . .the agency at this time is not intending to take regulatory action against those centers that, on the face of things, would not be complying with the new-drug requirements of the law."

Carol Marcus, PhD, MD, director of the nuclear medicine outpatient clinic, Harbor-University of California, Los Angeles Medical Center, and associate professor of radiological science, UCLA, said the FDA was basically "sticking to their proposal of last year," introduced during the November 1988 RDAC Meeting (see *Newsline*, February 1989, p. 137). During that meeting, Dr. Marcus had also proposed a plan for PET regulation, which had been endorsed by various members of The Society of Nuclear Medicine and the American College of Nuclear Physicians who were involved in leadership or radiopharmaceutical activities. Dr. Marcus said that while the FDA's statement that the Agency does not intend to interfere with the status quo at PET centers through regulatory action was somewhat comforting, the overall proposal is short-sighted and unrealistic.

Captain Briner said, "FDA is not any closer to approving PET than they were a year ago. . . although they have some ideas about how they'd like to do it, namely through the [investigational new drug] process."

During the RDAC Meeting, the Agency also reported on recent labeling changes in iodinated contrast media and proposed a restructuring of the RDAC.

Sarah M. Tilyou

RDAC Committee

Members

John Keyes, MD,
acting chairman
Victor M. Haughton, MD
Stanley J. Goldsmith, MD
Robert M. Allman, MD
Randall A. Hawkins, MD, PhD
A. Everette James, Jr., JD, MD
Mark M. Mishkin, MD
Charles M. Boyd, MD

Consultants

Barbara Y. Croft, PhD
H. William Strauss, MD
Capt. William H. Briner (ret.)
Ronald D. Finn, PhD