FDA Advisory Committee Finds In-111 Oxine Low Risk

The use of indium-111 oxine in labeling of blood cellular components poses no more risks than other substances used in diagnostic imaging, ruled the Food and Drug Administration's Advisory Committee on Radiopharmaceutical Drug Products. In addition, the committee found that indium-111 oxine offers certain advantages over other radionuclides.

At the November 9 meeting, committee member Carol S. Marcus, PhD, MD, reviewed data provided to the FDA that showed the risk—namely, "a remote risk of altering blood cells"—to be acceptable.

The question of risk has been debated ever since a team of scientists from the Netherlands published a report in 1983 which stated that "cytogenetic studies revealed that indium-111 oxinate induces severe chromosomal aberrations" in labeled lymphocytes that may cause a malignant process after proliferation. Dr. Marcus disagreed with their argument because the procedure affects mature, circulating lymphocytes, not the stem cells in marrow (*2*), and other researchers supported the use of indium-111 for blood labeling (*3*).

According to data provided to the FDA advisory committee by independent consultants, the best estimates of the risk of lymphocytic leukemia from this labeling technique are most probably several orders of magnitude less than the estimated risk of cancer from whole body radiation, said Dr. Marcus.

"Any risk must be compared to a potential benefit," explained Capt. William H. Briner, a consultant to the committee. "With indium-111 oxine, the benefits clearly outweigh the risk," added Capt. Briner, who is also chairman of The Society of Nuclear Medicine's Government Relations Committee.

In particular, indium-111 oxine should be used to trace possible unknown inflammatory lesions as "the properties of labeled blood cells cause them to localize in abnormal masses or cells, whereas with modalities such as CT or ultrasound you would have to do a whole-body survey if you didn't know where the masses were," explained Capt. Briner.

However, the FDA committee agreed that CT or ultrasound should be used first if the site of abscess is suspected or known.

The recommended dosage for indium-labeled leukocytes was set at 300 to 500 μCi, although a higher dosage may be needed in special clinical situations. Pediatric patients should be administered a lower dosage.

While no further studies on toxic effects are required, the committee recommended that firms which receive manufacturing approval should commit to Phase IV blood clearance and kinetic studies in both adult and pediatric patients.

The committee made several other decisions of interest to SNM members:

- New nuclear pharmacy guidelines establish criteria for determining when these pharmacies must register as a drug establishment, replacing the interim enforcement policy (*Federal Register* July 25, 1975).

As reported in the *Federal Register* of June 18, 1984, "The interim enforcement policy stated that the FDA would not take action against a nuclear pharmacy that fails to comply with the act, except when regulatory action is necessary to protect the public health, provided the nuclear pharmacy (1) complies with applicable local laws regulating the practice of pharmacy and (2) is licensed by the Nuclear Regulatory Commission or an agreement state, whichever is applicable, to possess, use, or transfer radioactive drugs. The agency adopted this interim enforcement policy to avoid any disruption in the practice of nuclear pharmacy and nuclear medicine pending clarification of the responsibilities of nuclear pharmacies under the act....

"With the availability of the guideline that sets forth criteria for determining when a nuclear pharmacy or similar establishment must register as a drug establishment, nuclear pharmacies may now determine their responsibilities under the act...."

"The new guidelines are totally acceptable to the SNM," said Capt. Briner. A copy of the guidelines can be obtained from the Division of Drug Labeling Compliance (HFN-310), Center for Drugs and Biologics, FDA, Rockville, MD 20857.

- Petitions to the FDA regarding labeling indications for three radiopharmaceuticals were discussed. All three—xenon-133 in saline for intradermal injection, Tc-99m-pertechnetate for instillation into the eye, and Tc-99m sulfur colloid for oral administration—are expected to be approved soon.
- The committee recommended establishing pediatric dosages for iodohippurate sodium and several other drugs.

References

1. ten Berge RJM, et al. Labeling with indium-111 has detrimental effects on human lymphocytes. *J Nucl Med* 24:615–620, 1983

2. Marcus CS. Letters to the editor. *J Nucl Med* 25:406–407, 1984

3. Thakur ML, McAfee JG. The significance of chromosomal aberrations in indium-111-labeled lymphocytes. *J Nucl Med* 25:922–927, 1984