FDA Panel Scrutinizes Thyroid Drug Stability

BY ELIZABETH MECHCATTIE Senior Writer

G A I T H E R S B U R G , M D . — A 10% loss in potency over the shelf life of levothyroxine sodium products—the maximum amount allowed under current regulations—raises clinically significant concerns, and current potency specifications for these products should be strengthened, according to Jane Duffy, the agency could follow the advice of its advisory panels, which are not binding. Jane Duffy, director of the division of postmarketing evaluation in the FDA’s Office of New Drug Quality Assurance. Therefore, the potential for a tablet to degrade is evident from the point where it contained less than 98% of its strength. For example, if a 150-mcg tablet lost 10% of its potency, it could contain the active ingredient, which is below the 137-mcg dose, the next lowest available dose; this actually occurred in two stability studies, Dr. Duffy said.

Because these studies were done under ideal situations, with controlled temperature and humidity, it can be assumed that the “real-life stability profile” of these products would not be any better than what was observed in these stability studies, he added. Levothyroxine tablets are typically subjected to a variety of factors that could affect stability, from the time the tablet is shipped from the manufacturer until it reaches the patient, with time spent in the warehouse, mailboxes, and pharmacies. Patients also store their tablets in various ways, often in a warm, moist environment such as a bathroom, but levothyroxine is not known to be stable only when stored unopened. And even after being controlled conditions in a sealed container, at or below room temperature, and kept dry.

“We have to ask for a higher set of standards” for a drug that comes in 12 dosage strengths and has such a narrow therapeutic index, said panelist Dr. Morris Schambelan, chief of the division of endocrinology at San Francisco General Hospital. Dr. Robert Tuttle, of the endocrine service at Memorial Sloan Kettering Cancer Center, New York, remarked that there was no “question” that a 10% change in dose would make a difference clinically in patients with thyroid cancer, who take levothyroxine under very controlled conditions.

Panelist Arthur Kibe, Ph.D., of the Nesbitt School of Pharmacy, Wilkes University, Wilkes-Barre, Pa., said that if the potency levels of all these products on the market were tightened, the possibility of differences between products would also be lessened and would reduce the chance of adverse effects of switching from one product to another.

Dr. Jurgen Venitz, of the Virginia Commonwealth University School of Pharmacy, Richmond, said that as much as he supported the panel’s recommendations, he felt that bioequivalence between products was really the bigger issue. One panelist referred to bioequivalence as “the 800-pound gorilla in the room.”

Speaking for AACE during the open public hearing, Dr. Jeffrey Garber, treasurer and chief of endocrinology at Harvard Vanguard Medical Associates, Boston, said that it had become “increasingly unlikely” that a patient would be given a therapeutically equivalent preparation, and that while the meeting was “a step in the right direction,” it did not address the broader issue of bioequivalence.

Speaking for the Endocrine Society, Dr. Leonard Wartofsky, president of the society, said that current FDA bioequivalence standards are not sensitive enough to detect small but meaningful differences between products, and that the FDA erred in allowing manufacturers to drop the warning that when a product is switched, patients need to call their physician and have their thyroid-stimulating hormone levels measured to titrate their dose. He referred to a May 2005 meeting cosponsored by the FDA, American Thyroid Association, Endocrine Society, and AACE to review concerns about substitution and bioequivalence, and concerns that one product may be substituted for another—often unknowingly to the physician—despite differences in potency.

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The last three patients in the series—who received the highest concentrated dose of ultrasound waves—showed complete coagulative necrosis in 75% of the targeted area. These patients also received local anesthesia.

“The intensity focused ultrasound allows us to destroy a very precise area,” Dr. Esmailt said. “It is an exciting procedure for thyroid nodule management, and it is a logical step when you are aware of technology.”

The HIFU treatment is done using real-time ultrasound imaging. The HIFU transducer emits a beam of convergent ultrasound waves toward the target tissue.

When the ultrasound waves first enter the tissue, the beam is wide, so the density is low and the waves do not damage the surrounding tissue. As the beam converges on the target, the density increases, and the tissue coagulates in a few seconds.

The beams are repeated at short intervals to achieve complete nodular destruction.

Overall, patients tolerated the treatment well. Seven patients experienced superficial skin blisters that subsequently healed, and the design of the treatment device has since been modified to reduce the risk of blistering, Dr. Esmailt said. Three patients chose to stop the treatment because they felt “uncomfortable or scarred.”

There was an increase in thyroglobulin in six cases at 1 day after the procedure, but the change was transient. No changes were observed in other thyroid hormones, including T3 and T4, as a result of HIFU.

Caveats of the study included the fact that some patients got stronger doses of ultrasound than others. “It was not always possible to deliver the right energy amount for maximum efficiency, due to slight skin breaks,” Dr. Esmailt said.

But data from additional patients who have been treated in this ongoing phase II study confirm that skin tolerance is good at high energy levels, he added.

Although the HIFU treatment has been used only on benign thyroid nodules so far, HIFU is used to treat prostate cancer, and it can probably be used to treat thyroid cancer in the future, Dr. Esmailt said. “We just treated benign nodules, so we didn’t worry about margins, but if you need a margin you can obtain it,” he said. A big difference between HIFU and other ablative techniques is the high degree of precision that HIFU requires, he added.

The researchers have not studied the DNA or any other characteristics of the nondestroyed tissue surrounding any of the HIFU-treated nodules to look for adverse effects, but the pathologist did not observe any changes in the surrounding tissue, he noted.

Results from a literature review published in 2003 suggested that high-intensity focused ultrasound may have a significant impact on all fields of surgery, including thyroid surgery (Br J Radiol. 2003;76:390-9). Although a controlled study and long-term follow-up are necessary next steps, these early findings help establish safety, efficacy, and the treatment parameters for the use of HIFU on benign thyroid nodules, Dr. Esmailt said.

Dr. Esmailt has an ownership interest in Theracision, the manufacturer of the HIFU that was used in the study.