



A message to Members and Colleagues of the American Thyroid Association

On May 24, 2010, Genzyme Corp. entered into a Consent Decree of Permanent Injunction with the United States Food and Drug Administration (FDA) to resolve litigation in which the FDA has alleged that Genzyme manufactured, labeled, and distributed drugs at its Allston, Massachusetts facility in violation of current good manufacturing practice requirements for drugs.

During an inspection of the Allston plant from Oct. 8, 2009, until Nov. 13, 2009, FDA inspectors found that the company's systems for ensuring manufacturing quality were inadequate, resulting in production delays, critical shortages of medically necessary products to consumers and drugs contaminated with metal, fiber, rubber and glass particles. These manufacturing problems violated the FDA's regulations for manufacturing practice. To date, these violations have not been associated with reports of adverse events in patients.

In the consent decree, Genzyme has agreed to correct manufacturing quality violations and will turn over to the federal government \$175 million in profits from the sale of products made at the plant. In addition, the consent decree requires Genzyme to move fill/finish operations out of the Allston plant for Cerezyme, Fabrazyme and Thyrogen sold within the United States by November 28, 2010, and by August 31, 2011 for products sold outside of the United States. Should Genzyme not meet these deadlines, the FDA can require the company to repay 18.5 percent of revenue from these products.

The consent decree is designed to permit Genzyme to provide for the United States market enough Thyrogen (recombinant human TSH) to meet the needs of patients for whom FDA considers the drug to be medically necessary. This restriction will remain in place until Genzyme transfers fill/finish manufacturing operations to other manufacturing facilities operating in compliance with FDA regulations. This decree does not affect the availability of Thyrogen outside of the US.

The FDA has developed a set of criteria to help healthcare professionals identify patients for whom Thyrogen is considered medically necessary. Importantly, the FDA expects physicians to make this determination, but physicians are not being required to individually certify medical necessity. This action is expected to minimize the burden of the consent decree on the practicing physician. According to the FDA, the following criteria should be met for Thyrogen to be considered medically necessary for a patient with thyroid cancer:

1. Patients undergoing initial radioiodine ablation of thyroid tissue remnants, post-thyroidectomy, deemed to be at significantly increased risk of side-effects/complications from undergoing thyroid hormone withdrawal.

Patients deemed to be at significantly increased risk of side-effects or complications from undergoing thyroid hormone withdrawal for purposes of the criteria above are:

- Patients with history of stroke, transient ischemic attack, or underlying heart disease, especially heart failure that may be exacerbated by hypothyroidism (NYHA class III or IV).

- Patients with renal failure (National Kidney Foundation stage ≥ 3) in whom prolonged hypothyroidism will affect clearance of radioactive iodine.
- Patients with a history of or active psychiatric disorders (e.g., depression) that will be exacerbated by hypothyroidism.
- Patients whose overall performance status may be severely compromised during hypothyroidism (e.g., ECOG performance status ≥ 2).
- Patients on medications with a narrow therapeutic index (e.g., digoxin, lithium, warfarin) for which clearance of medications may be impaired by hypothyroidism.
- Patients with hypopituitarism or who have previously been unable to mount an adequate increase in endogenous thyroid stimulating levels (TSH) levels.
- Patients > 65 years of age regardless of the presence or absence of other concurrent medical conditions.

Generally, pediatric patients are not considered to be within the medically necessary category as they are more likely to tolerate a short period of hypothyroidism and can often mount an adequate elevation of endogenous TSH within two weeks of levothyroxine withdrawal.

2. Follow-up testing of patients considered high risk for thyroid cancer recurrence and who have unmeasurable basal thyroglobulin (Tg) levels and are deemed to be at significantly increased risk of side-effects/complications from undergoing thyroid hormone withdrawal.

The [American Thyroid Association's 2009 Guidelines \(PDF - 728KB\)](#)¹ provide a three-level stratification for assessment of risk of thyroid cancer recurrence and identify as "high-risk" those patients who have:

- a) macroscopic tumor invasion,
- b) incomplete tumor resection,
- c) distant metastases, and possibly
- d) thyroglobulinemia out of proportion to what is seen on the post-treatment scan.

3. Initial rTSH stimulation testing in patients not considered high risk for thyroid cancer recurrence may also be considered appropriate if such patients are at-risk of side-effects/complications from prolonged hypothyroidism due to thyroid hormone withdrawal.

The ATA will continue to monitor the availability of Thyrogen and provide more details for our members and colleagues as they become available.

Additional information is available at:

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm213212.htm>

<http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm213008.htm>

American Thyroid Association
 6066 Leesburg Pike, Suite 550
 Falls Church, VA 22041-2222
 Phone: 703.998.8890
 Email: thyroid@thyroid.org