Clinical Policy Bulletin:
Thyrogen (Thyrotropin Alfa)

Number: 0515

Policy

Aetna considers administration of Thyrogen (thyrotropin alfa) medically necessary for the following groups with a history of differentiated thyroid carcinoma:

I. For thyroglobulin (Tg) testing and radioiodine imaging in place of thyroid hormone withdrawal for any of the following groups:

   A. Members in whom withdrawal from hormone supplement is contraindicated for medical reasons; or
   B. Members requiring serum Tg testing and radioiodine imaging who are unwilling to undergo thyroid hormone withdrawal testing and whose treating physician believes that use of a less sensitive test is justified; or
   C. Members who are either unable to mount an adequate endogenous thyroid stimulating hormone (TSH) response to thyroid hormone withdrawal; or
   D. Members who would otherwise be examined solely with a serum Tg test without undergoing hormone supplement withdrawal; or
   E. Members with an undetectable Tg on thyroid hormone suppressive therapy to exclude the diagnosis of residual or recurrent thyroid cancer.

II. To facilitate radioiodine ablation of remnant thyroid tissue after surgery for differentiated thyroid carcinoma, as an alternative to thyroid hormone withdrawal.

III. As an adjunct to radioiodine ablation for the treatment of non-toxic multinodular goiter.

Aetna considers thyrotropin alfa experimental and investigational for all other indications (e.g., for individuals with differentiated thyroid cancer, and who have suppressed serum thyroglobulin [less than 0.1 ng/ml]) because of insufficient evidence of effectiveness.
Note: Periodic thyroid hormone withdrawal Tg testing, with or without radioiodine imaging, still remains the standard diagnostic modality to assess the presence, location and extent of thyroid cancer in persons who have undergone surgery or radioactive iodine treatment.

Background

Surgery is the cornerstone of management of patients with differentiated thyroid cancer. As an adjunct to this treatment, some high-risk patients may need to undergo radioactive iodine treatment, further destroying normal thyroid tissue. All patients with tumors arising from follicular epithelium require thyroid stimulating hormone (TSH) suppression since differentiated thyroid cancers contain membrane receptors responsive to TSH. Long-term thyroid hormone supplements are used to maintain metabolism in patients who have had partial or total thyroidectomy and/or radioactive iodine treatment and to suppress endogenous levels of TSH.

Management of patients with a history of thyroid carcinoma requires continuing evaluation to monitor cancer recurrence and metastatic disease by periodic physical examinations, thyroglobulin levels, radioiodine scans, and assurance of appropriate TSH suppression. A high level of TSH in a patient's bloodstream is necessary to achieve optimal sensitivity of serum thyroglobulin testing and in order for radioiodine imaging to detect remnant thyroid tissue or metastatic disease. In order to accomplish this, patients must stop taking their hormone supplements for two to six weeks prior to testing. This thyroid hormone withdrawal causes patients to experience symptoms of hypothyroidism -- fatigue, weight gain, constipation, mental dullness, lethargy, depression, and other adverse reactions.

On December 1, 1998, the Food and Drug Administration (FDA) granted marketing approval for Thyrogen (thyrotropin alfa) for use as "an adjunctive diagnostic tool for serum thyroglobulin testing with or without radioiodine imaging in the follow-up of patients with well-differentiated thyroid cancer." Thyrogen, a recombinant form of TSH, provides an external source of TSH and allows thyroid cancer patients to avoid hormone withdrawal and its debilitating effects while undergoing diagnostic testing.

The FDA made its decision based on review of 2 phase III clinical trials, which were conducted on 358 patients with well-differentiated thyroid cancer to compare 48-hour radioiodine whole body scans obtained after Thyrogen to whole body scans after thyroid hormone withdrawal. One of these trials also compared thyroglobulin levels obtained after Thyrogen to those on thyroid hormone suppression therapy, and to those after thyroid hormone withdrawal. Across the 2 clinical studies, Thyrogen was shown to significantly enhance the sensitivity of thyroglobulin testing in patients maintained on thyroid hormone therapy. The combination of a Thyrogen-stimulated scan and a serum thyroglobulin test did detect all patients with metastatic disease, although not as sensitive as combination testing performed after patients were withdrawn from thyroid hormone supplements. The Thyrogen-stimulated scan failed to detect remnant and/or cancer localized to the thyroid bed in 16 % (20/124) of patients in whom it was
detected by a scan after thyroid hormone withdrawal. In addition, the Thyrogen scan failed to detect metastatic disease in 24% (9/38) of patients in whom it was detected by a scan after thyroid hormone withdrawal. Based on these studies, it can be concluded that even when Thyrogen-stimulated thyroglobulin testing is performed in combination with radioiodine imaging, there remains a meaningful risk of missing a diagnosis of thyroid cancer or of under-estimating the extent of disease.

Recombinant human thyrotropin has also been demonstrated to be useful to facilitate radioiodine ablation of remnant thyroid tissue after surgery for differentiated thyroid carcinoma, as an alternative to thyroid hormone withdrawal. After surgery for differentiated thyroid carcinoma, many patients are treated with radioiodine to ablate remnant thyroid tissue. This procedure is most commonly performed with the patient in the hypothyroid state to promote endogenous TSH stimulation to optimize radioiodine uptake by remnant thyroid tissue. However, thyroid hormone withdrawal is associated with hypothyroid symptoms and impaired quality of life. Pacini et al (2006) reported the results of a randomized controlled clinical trial to compare recombinant human thyrotropin to prepare patients on thyroid hormone therapy to ablate remnant thyroid tissue with radioiodine, compared with conventional remnant ablation performed in the hypothyroid state. The investigators found comparable remnant ablation rates by administering recombinant human thyrotropin or by withholding thyroid hormone. Successful thyroid remnant ablation was achieved by 23 of 24 patients (96%) treated with recombinant human thyrotropin, compared to 18 of 21 (86%) patients treated in the hypothyroid state (p = 0.23). These investigators reported that subjects treated with recombinant human thyrotropin had a significantly higher quality of life during treatment than subjects treated in the hypothyroid state. They reported that subjects treated with recombinant human thyrotropin also had a significantly lower radiation exposure to the blood than patients treated in the hypothyroid state.

Mallick et al (2012) noted that it is not known whether low-dose radioiodine (1.1 GBq [30 mCi]) is as effective as high-dose radioiodine (3.7 GBq [100 mCi]) for treating patients with differentiated thyroid cancer or whether the effects of radioiodine (especially at a low-dose) are influenced by using either thyrotropin alfa or thyroid hormone withdrawal. At 29 centers in the United Kingdom, these researchers conducted a randomized non-inferiority trial comparing low-dose and high-dose radioiodine, each in combination with either thyrotropin alfa or thyroid hormone withdrawal before ablation. Patients (age range of 16 to 80 years) had tumor stage T1 to T3, with possible spread to nearby lymph nodes but without metastasis. End points were the rate of success of ablation at 6 to 9 months, adverse events, quality of life, and length of hospital stay. A total of 438 patients underwent randomization; data could be analyzed for 421. Ablation success rates were 85.0% in the group receiving low-dose radioiodine versus 88.9% in the group receiving the high-dose and 87.1% in the thyrotropin alfa group versus 86.7% in the group undergoing thyroid hormone withdrawal. All 95% confidence intervals for the differences were within +/- 10 percentage points, indicating non-inferiority. Similar results were found for low-dose radioiodine plus thyrotropin alfa (84.3%) versus high-dose radioiodine plus thyroid hormone withdrawal (87.6%) or high-dose radioiodine plus thyrotropin alfa (90.2%). More patients in the high-dose group than in the low-dose group were hospitalized for at least 3 days (36.3...
% versus 13.0 %, p < 0.001). The proportions of patients with adverse events were
21 % in the low-dose group versus 33 % in the high-dose group (p = 0.007) and 23
% in the thyrotropin alfa group versus 30 % in the group undergoing thyroid
hormone withdrawal (p = 0.11). The authors concluded that low-dose radioiodine
plus thyrotropin alfa was as effective as high-dose radioiodine, with a lower rate of
adverse events.

Rosario et al (2012) evaluated the effectiveness of recombinant human thyroid
stimulating hormone [rhTSH (versus hypothyroidism)] in thyroid ablation with an
activity of 1.1 GBq (30 mCi) (131)I. A total of 102 patients with thyroid cancer who
fulfilled the following criteria were studied: submitted to total thyroidectomy with
complete tumor resection; tumor less than or equal to 4 cm without extra-thyroid
invasion or lymph node metastases; negative anti-thyroglobulin (anti-Tg)
antibodies. Thirty-two patients (group A) received 0.9 mg of rhTSH for 2
consecutive days followed by (131)I administration and 70 patients (group B) were
prepared by levothyroxine withdrawal for 4 weeks. The groups were similar in sex,
age, and tumor characteristics. Ablation was successful (stimulated Tg less than 1
ng/ml and negative diagnostic whole-body scanning and neck ultrasonography 9
to 12 mo after ablation) in 27 patients of group A (84.3 %) and in 58 of group B (83
%). Considering patients with Tg greater than 1 ng/ml immediately before (131)I
administration, the rates were 72.2 % in group A and 75 % in group B. In group A,
the ablation rate was similar for patients who discontinued levothyroxine-T4 3 days
before (131)I administration and those maintained on hormone therapy. The
mean follow-up was 29.6 months in group A and 55 months in group B. Stimulated
Tg (after rhTSH) was undetectable in 29 patients of group A (90.6 %) and in 61 of
group B (87 %) and 1 patient of group B presented cervical metastases at the last
assessment. The authors concluded that low (131)I activity after rhTSH is
effective for remnant ablation in patients who are at low-risk of recurrence.

Fast et al (2012) evaluated the long-term outcome of rhTSH-augmented
radioiodine ((131)I) therapy for benign multi-nodular non-toxic goiter. Between
2002 and 2005, a total of 86 patients with a multi-nodular non-toxic goiter were
treated with (131)I in 2 randomized, double-blind, placebo-controlled trials. (131)I-
therapy was preceded by 0.3 mg rhTSH (n = 42) or placebo (n = 44). In 2009, 80
patients completed a follow-up (FU) visit, including determination of thyroid
volume, thyroid function, and patient satisfaction by a visual analog scale (VAS). In
both groups, thyroid volume was further reduced from 1 year to final FU (71
months). The mean goiter volume reductions obtained at 1 year and final FU [59.2
+/- 2.4 % (sem) and 69.7 +/- 3.1 %, respectively] in the rhTSH group were
significantly greater than those obtained in the (131)I-alone group (43.2 +/- 3.7 and
56.2 +/- 3.6 %, respectively, p = 0.001 and p = 0.006), corresponding to a gain of
24 % at final FU. At last FU, the mean reduction in compression VAS was
significantly greater in patients receiving rhTSH (p = 0.049). Additional therapy
(thyroid surgery or (131)I) was required more often in the placebo group (9 of 44)
compared with the rhTSH group (2 of 42) (p = 0.05). The prevalence of
hypothyroidism at 1 year [9 and 43 % in the placebo and rhTSH groups,
respectively (p < 0.0001)] increased to 16 and 52 %, respectively, at final FU (p =
0.001). The authors concluded that enhanced goiter volume reduction with rhTSH
-augmented (131)I therapy improved the long-term reduction in goiter-related
symptoms and reduced the need for additional therapy compared with plain (131)I
therapy. They noted that overall patient satisfaction was benefited despite a higher rate of permanent hypothyroidism.

An UpToDate review on “Diagnostic approach to and treatment of goiter in adults” (Ross, 2013) states that “Pretreatment with recombinant human TSH (rhTSH, thyrotropin alpha) increases radioiodine uptake in nontoxic nodular goiter, and results in a more homogeneous distribution of uptake by stimulating uptake in relatively cold areas more than in relatively hot areas, particularly in those with low serum TSH concentrations. Thus, administration of rhTSH allows for treatment with lower doses of radioiodine without compromising efficacy. It has been shown to be a useful adjunct to radioiodine for the treatment of nontoxic multinodular goiter, especially when the radioiodine uptake is low. The proposed dose of rhTSH is much lower than is used for treatment and diagnostic testing in patients with thyroid cancer”.

Chindris et al (2012) noted that surveillance of patients with differentiated thyroid cancer (DTC) is achieved using serum Tg, neck ultrasonography (US), and rhTSH-stimulated Tg (Tg-stim). These investigators assessed the utility of rhTSH Tg-stim in patients with suppressed Tg (Tg-supp) below 0.1 ng/ml using a sensitive assay. The secondary aims were to assess the utility of US and to summarize the profile of subsequent Tg-supp measures. A total of 163 patients (status: after thyroidectomy and radioactive iodine treatment) who had Tg-supp below 0.1 ng/ml and rhTSH Tg-stim within 60 days of each other were included. After rhTSH stimulation, Tg remained below 0.1 ng/ml in 94 (58 %) and increased to 0.1 to 0.5 in 56 (34 %), more than 0.5 to 2.0 in 9 (6 %), and above 2.0 ng/ml in 4 (2 %) patients. Serial Tg-supp levels were obtained in 138 patients followed over a median of 3.6 years. Neck US was performed on 153 patients; suspicious examinations had fine-needle aspiration (FNA). All positive FNA were identified around the time of the initial rhTSH test; 6 of 7 recurrences were detected by US (Tg-stim greater than 2.0 ng/ml in 1, 0.8 in 1 and less than or equal to 0.5 in 4). One stage IV patient had undetectable Tg-stim. The authors concluded that in patients with DTC whose T(4)-suppressed serum Tg is below 0.1 ng/ml, long-term monitoring with annual Tg-supp and periodic neck US are adequate to detect recurrences. In the authors’ experience, rhTSH testing does not change management and is not needed in this group of patients.

**CPT Codes / HCPCS Codes / ICD-9 Codes**

**Other CPT codes related to the CPB:**

78012
78013
78014
78015 - 78018
+ 78020
HCPCS codes covered if selection criteria are met:

J3240  Injection, thyrotropin alpha, 0.9 mg, provided in 1.1 mg vial

ICD-9 codes covered if selection criteria are met:

193  Malignant neoplasm of thyroid gland

V10.87  Personal history of malignant neoplasm of thyroid

The above policy is based on the following references:


