Getting to Know Thyrogen® (thyrotropin alfa for injection)

IMPORTANT SAFETY INFORMATION (continued)

Patients over 65 years old with large amounts of leftover thyroid tissue after surgery, or with a history of heart disease, should discuss with their physicians the risks and benefits of Thyrogen.

Thyrogen can be administered in the hospital for patients at risk for complications from Thyrogen administration. Since Thyrogen was first approved for use, there have been reports of central nervous system problems such as stroke in young women who have a higher chance of having a stroke, and weakness on one side of the body.

Patients should remain hydrated prior to treatment with Thyrogen.

Leftover thyroid tissue after surgery and cancer cells that have spread to other parts of the body can quickly grow and become painful after Thyrogen administration.

Patients with cancer cells near their windpipe, in their central nervous system, or in their lungs may need treatment with a glucocorticoid (a medication to help prevent an increase in the size of the cancer cells before using Thyrogen.)

ADVERSE REACTIONS

In clinical studies, the most common side effects reported were nausea and headache.

USE IN SPECIFIC PATIENT POPULATIONS

Pregnant patients: Thyrogen should be given to a pregnant woman only if the doctor thinks there is a clear need for it.

Breastfeeding patients: It is not known whether Thyrogen can appear in human milk. Breastfeeding women should discuss the benefits and risks of Thyrogen with their physician.

Children: Safely and effectiveness in young patients (under the age of 18) have not been established.

Elderly: Studies do not show a difference in the safety and effectiveness of Thyrogen between adult patients less than 65 years and those over 65 years of age.

Patients with kidney disease: Thyrogen exits the body much slower in dialysis patients and can lead to longer high TSH levels.

INDICATIONS

Thyrogen is used to help identify thyroid disease by testing the blood for a hormone called thyroglobulin in the follow up of patients with a certain type of thyroid cancer known as well differentiated thyroid cancer. It is used with or without a radiology test using a form of iodine.

Limitations of Use:

• The effect of Thyrogen on long term thyroid cancer outcomes has not been determined.

• When Thyrogen is used to help detect thyroid cancer, there is still a chance all or parts of the cancer could be missed.

Thyrogen is also used to help patients prepare for treatment with a form of iodine, called radioiodine, to remove leftover thyroid tissue in patients who have had surgery to take out the entire thyroid gland for patients with well differentiated thyroid cancer who do not have signs of thyroid cancer which has spread to other parts of the body.

Limitations of Use:

• In a study of people being prepared for treatment with a form of iodine after thyroid surgery, results were similar between those who received Thyrogen and those who stopped taking their thyroid hormone for up to five years after treatment. Researchers do not know if results would be similar over a longer period of time.

The Thyrogen Patient Kit provides important information for patients with thyroid cancer, post total thyroidectomy.

Please discuss the contents of this kit with your healthcare provider.

Thyrogen® (thyrotropin alfa) for intramuscular use

IMPORTANT SAFETY INFORMATION

Patients should not use Thyrogen with radioiodine if they have a contraindication to the use of radioiodine. Please consult with your doctor for a list of contraindications for radioiodine.

Thyrogen can cause serious side effects, including:

Thyrogen-Induced Hyperthyroidism:
There have been reports of events that led to death in patients who not had surgery to have their thyroid gland removed, and in patients with thyroid cancer cells that have spread to other parts of the body.

Patients over 65 years old with large amounts of leftover thyroid tissue after surgery, or with a history of heart disease, should discuss with their physicians the risks and benefits of Thyrogen.

Thyrogen can be administered in the hospital for patients at risk for complications from Thyrogen administration.

Stroke:
Since Thyrogen was first approved for use, there have been reports of central nervous system problems such as stroke in young women who have a higher chance of having a stroke, and weakness on one side of the body. The relationship between THYROGEN administration and stroke is unknown. Patients should remain hydrated prior to treatment with Thyrogen.

Sudden Rapid Tumor Enlargement:
Leftover thyroid tissue after surgery and cancer cells that have spread to other parts of the body can quickly grow and become painful after Thyrogen administration. Patients with cancer cells near their windpipe, in their central nervous system, or in their lungs may need treatment with a glucocorticoid (a medication to help prevent an increase in the size of the cancer cells before using Thyrogen.)

Risks Associated with Radioiodine Treatment:
If THYROGEN is administered with radioiodine (RAI), the serious side effects for RAI apply to this combination regimen. Please consult with your doctor for a list of contraindications for radioiodine.

ADVERSE REACTIONS

In clinical studies, the most common side effects reported were nausea and headache.

USE IN SPECIFIC PATIENT POPULATIONS

Pregnant patients: Notify your healthcare provider immediately in the event of a pregnancy. If THYROGEN is administered with radioiodine, the combination regimen should not be used in pregnant women. Thyrogen should be given to a pregnant woman only if the doctor thinks there is a clear need for it.

Breastfeeding patients: If THYROGEN is administered with radioiodine, the combination regimen should not be used in breastfeeding women. It is not known whether Thyrogen can appear in human milk. Breastfeeding women should discuss the benefits and risks of Thyrogen with their physician.

Children: Safety and effectiveness in young patients (under the age of 18) have not been established.

Elderly: Studies do not show a difference in the safety and effectiveness of Thyrogen between adult patients less than 65 years and those over 65 years of age.

Patients with kidney disease: Thyrogen exits the body much slower in dialysis patients and can lead to longer high TSH levels.

PLEASE SEE ENCLOSED FULL PRESCRIBING INFORMATION
Dear Patient,

This kit was created by Genzyme Corporation (“Sanofi Genzyme”), the makers of Thyrogen® (thyrotropin alfa), to help you as you begin therapy.

Thyrogen is used to help prepare patients for a treatment to remove leftover thyroid tissue as well as for certain diagnostic tests to monitor for the recurrence of thyroid cancer.

During the preparation phase, Thyrogen allows you to stay on your thyroid hormone medication and helps avoid the signs and symptoms of hypothyroidism.

This kit provides the following information and resources for you on your journey:

- Information about the uses of Thyrogen for patients with well-differentiated thyroid cancer is provided on the printed folder.
- What is Thyrogen? a comprehensive overview of Thyrogen, a medication prescribed by your doctor
- Elements of the Thyroid Cancer Journey includes some of the most common steps in the evaluation and treatment of well-differentiated thyroid cancer
- Help Avoid the Signs & Symptoms of Hypothyroidism explains some of the common symptoms of hypothyroidism and how Thyrogen can help
- The Thyrogen Administration Schedule shows you how Thyrogen is prescribed for use in preparation for remnant ablation or follow-up testing. This includes space for you and your healthcare provider to add in date, time and location for therapy you have been prescribed
- Post-treatment Information for Radioiodine Therapy contains information from the American Thyroid Association on tips to follow after treatment
- Thyrogen Financial Assistance provides information on co-pay and financial assistance programs to help you access Thyrogen as prescribed by your doctor
- The Low-Iodine Diet Card has tips for low-iodine foods for use as recommended by your healthcare provider in preparation for remnant ablation or follow-up testing

Of course, your healthcare provider is your most important resource to determine the best treatment for you. Ask your doctor if you have any questions about Thyrogen or your thyroid cancer journey.

We hope this information is helpful to you.

INDICATIONS AND USAGE
Thyrogen is used to help identify thyroid disease by testing the blood for a hormone called thyroglobulin in the follow up of patients with a certain type of thyroid cancer known as well differentiated thyroid cancer. It is used with or without a radiology test using a form of iodine.

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Limitations of Use:
- In a study of people being prepared for treatment with a form of iodine after thyroid surgery, results were similar between those who received Thyrogen and those who stopped taking their thyroid hormone for up to 5 years after treatment. Researchers do not know if results would be similar over a longer period of time.

PLEASE SEE ENCLOSED FULL PRESCRIBING INFORMATION
For Patients with Low- and Intermediate-Risk Differentiated Thyroid Cancer

There are many ways to access thyroid cancer after thyroidectomy. One of them is called the Orlov protocol. Talk to your doctor to determine which tests are right for you.²

Surgery
Total or partial removal of thyroid gland depends on:

• Size of tumor(s)
• Type of tumor cells
• Extension beyond the thyroid and lymph node involvement

Thyroid Hormone Replacement Therapy
• Because all or part of your thyroid is removed during surgery, thyroid hormone replacement therapy may be necessary

• Thyroid hormone replacement therapy enables you to function as if you still had your thyroid and controls/lowers your thyroid stimulating hormone (TSH) blood levels
• Thyroid hormone medication is taken for life and checked regularly

Evaluation Approximately 3-8 Weeks After Surgery¹,²
An example of evaluation after surgery, to help determine your treatment plan, may be:

Some tests that may be used to help guide your treatment plan include thyroglobulin, whole-body scan, neck ultrasound and TSH blood test.

Stimulated Thyroglobulin Blood Test and Neck Ultrasound

Evaluate Stimulated Thyroglobulin Levels²

Low
Intermediate
Elevated

No Routine Radioactive Iodine Ablation
Possible Radioactive Iodine Ablation
Probable Radioactive Iodine Ablation

Your doctor may consider other factors when recommending treatment plans (such as age, tumor type, etc.)

Radioactive Iodine Ablation

• Used to destroy any remaining normal or (if present) cancerous thyroid cells following surgery
• Taken by mouth usually in capsule form
• Take precautions following the use of radioactive iodine
• Given approximately 4-12 weeks after surgery, depending on your evaluation

Assessment of Status 6-18 Months After Initial Treatment

• May include tests such as such as thyroglobulin blood test, neck ultrasound, and whole-body scan, (ask your doctor what tests are right for you)
• May also receive a stimulated thyroglobulin test to verify absence of disease
• Thyroglobulin blood testing may be repeated every 12 months
• Whole-body scan may provide additional information

How you respond to initial treatment guides the intensity of future treatment and monitoring


Each patient journey is unique. Please talk to your doctor to understand the treatment options available to you.
Each patient journey is unique. Please talk to your doctor to understand the treatment options available to you.
If you have been diagnosed with well-differentiated thyroid cancer,

Ask your doctor or nurse for a copy of Sanofi Genzyme’s pamphlet “Understanding Well-Differentiated Thyroid Cancer.” Additional resources for well-differentiated thyroid cancer information are also provided on Sanofi Genzyme’s web site at www.thyrogen.com.

Regular communication with your doctor or health care provider about your medical condition will help make sure that you are getting appropriate care. Sanofi Genzyme, the makers of Thyrogen® (thyrotropin alfa), can help answer the questions you may have about Thyrogen.

Treatment

If you have been diagnosed with well-differentiated thyroid cancer your physician will need to consider the most appropriate treatment. For most patients, surgery is performed to remove all or part of the thyroid gland. However, surgery may not remove 100% of the thyroid tissue in your neck. Removal of all thyroid tissue aids follow-up and could reduce the risk of recurrence of thyroid cancer. To destroy this remaining tissue, another procedure called Radioactive Iodine (RAI) ablation may play a key role in the treatment and diagnostic evaluation in the management of well-differentiated thyroid cancer patients.

In order to prepare you for RAI ablation, your remaining thyroid tissue must be stimulated to aid the absorption of the RAI that you ingest, in the form of a pill or liquid. Stimulation can be achieved in two ways. The first method, withholding thyroid hormone replacement therapy, allows thyroid hormone levels to drop allowing thyroid-stimulating hormone (TSH) levels to increase before RAI ablation. However, this method makes you hypothyroid.

The second option involves the use of Thyrogen® (thyrotropin alfa), a recombinant human form of TSH, which can be used as part of the RAI ablation treatment process. In essence, Thyrogen allows your physician to start you on thyroid hormone replacement therapy right after your surgery, helping to avoid some of the signs and symptoms of hypothyroidism. Both methods, using Thyrogen and increasing TSH by withholding thyroid hormone replacement therapy, have shown comparable success rates in thyroid remnant ablation.

Well-differentiated thyroid cancer follow-up

Follow-up visits with your doctor are essential to determine if any thyroid cancer remains or has returned—and if so, to ensure that you receive additional treatment. To test for a recurrence of thyroid cancer, your doctor will want to perform testing. In order to obtain the most reliable diagnostic test results to detect thyroid cancer recurrence, thyroid-stimulating hormone (TSH) must be at high levels in the bloodstream. This triggers any remaining thyroid cancer cells and normal thyroid cells to make thyroglobulin (Tg), a substance that can be tested in the blood, and to better absorb radioiodine which can be seen on specialized x-rays such as a whole body scan (WBS).

One option to increase your TSH levels is by stopping your thyroid hormone replacement therapy (thyroid hormone withdrawal) which will cause hypothyroidism (thyroid hormone replacement therapy keeps TSH levels low). Symptoms of hypothyroidism can continue after restarting thyroid hormone replacement therapy until the thyroid hormone level is back to normal. The other option for increasing TSH levels is by using Thyrogen® (thyrotropin alfa). Thyrogen is the only way to raise your TSH without having to stop taking thyroid hormone replacement therapy.
What is Thyrogen® (thyrotropin alfa) and what does it do?

Thyrogen® (thyrotropin alfa), produced using a biotechnology process, is a protein whose properties are similar to natural human thyroid-stimulating hormone (TSH). Thyrogen is given by intramuscular injection prior to RAI ablation or diagnostic testing in patients with well-differentiated thyroid cancer.

Thyrogen helps you to avoid hypothyroidism while still allowing your physician to treat the thyroid remnant in patients who do not have signs of thyroid cancer that has spread to other parts of the body (distant metastases). It can also help obtain reliable diagnostic test results for the recurrence of well-differentiated thyroid cancer.

With Thyrogen® (thyrotropin alfa), you can keep taking your thyroid hormone replacement therapy while being tested for well-differentiated thyroid cancer recurrence.

When might my doctor recommend Thyrogen® (thyrotropin alfa)?

- Thyrogen permits your doctor to put you on thyroid hormone replacement therapy right after surgery and prior to RAI ablation.
- Thyrogen treatment may be used in combination with radioiodine to remove thyroid remnants following near-total or total thyroidectomy in patients without evidence of distant metastatic disease (outside the neck).
- If a previous Tg blood test was negative while you were taking thyroid hormone replacement therapy, your doctor may want to confirm this result with a stimulated Tg blood test in combination with Thyrogen.

What are the possible side effects with Thyrogen?

The most common side effects reported in clinical studies were nausea, headache, fatigue, vomiting and dizziness. In post-approval experience flu-like symptoms and allergic reactions (hypersensitivity) were reported by patients. Seek immediate medical attention if you experience any severe symptoms.

Even with a Thyrogen-stimulated Tg test and whole body scan, a risk remains of missing a diagnosis of thyroid cancer or of underestimating the extent of disease. If you have any questions or concerns, you should talk with your doctor before or after receiving Thyrogen.

What should I tell my doctor before receiving Thyrogen?

Tell your doctor if you are pregnant, planning to become pregnant or breast feeding.
Tell your doctor if you have or have had any problems with your kidneys.

Is there any other important information I should know before receiving Thyrogen?

Patients over 65 years old with large amounts of leftover thyroid tissue after surgery, or with a history of heart disease, should discuss with their physicians the risks and benefits of Thyrogen.

Thyrogen can be administered in the hospital for patients at risk for complications from Thyrogen administration.

Since Thyrogen was first approved for use, there have been reports of central nervous system problems such as stroke in young women who have a higher chance of having a stroke, and weakness on one side of the body. Seek immediate medical attention if you experience any of these symptoms after receiving Thyrogen.

Patients should remain hydrated prior to treatment with Thyrogen.

PLEASE SEE ENCLOSED FULL PRESCRIBING INFORMATION
Thyrogen® (thyrotropin alfa) administration was not associated with the signs and symptoms of hypothyroidism that accompanied thyroid hormone withdrawal.

In a study of 229 thyroidectomized patients with well-differentiated thyroid cancer, undergoing whole-body scans, thyroid hormone withdrawal (stopping thyroid hormone medication) was compared to Thyrogen. Thyrogen patients had less signs and symptoms of hypothyroidism than those who underwent thyroid hormone withdrawal.

The signs and symptoms were measured by using a Billewicz scale. A Billewicz scale is an observer-rated set of clinical findings that has been widely used in assessing hypothyroidism. Higher scores are associated with a decrease in quality of life.

**How did Thyrogen compare with thyroid hormone withdrawal in these studies?**

There were three sets of scores taken:
- For all patients during the pre-treatment phase when they were on thyroid hormone treatment.
- For the patients who took Thyrogen
- For the patients who were withdrawn from thyroid hormone replacement treatment

The chart below shows that patients who took Thyrogen did not experience any of the symptoms of hypothyroidism. However, the patients who went through thyroid hormone withdrawal experienced significantly worse signs and symptoms in all the parameters measured in the study.

The Billewicz scale is used by observers to assess hypothyroidism, based on a set of 14 signs and symptoms.
Thyrogen® (thyrotropin alfa)
Administration Schedule

Thyrogen is given as an injection into the muscle of the buttock for two days in a row. These injections are given by a health care provider. If you are receiving Thyrogen for ablation or diagnostic testing the following schedule may be used:

Your Thyrogen ablation checklist and schedule (to be filled out by your doctor or nurse)

Follow a low-iodine diet before ablation therapy
☐ Start low-iodine diet on _______  ☐ End low-iodine diet on _______
☐ You will receive two Thyrogen injections. The dates, times and location for your appointments are listed on the schedule below.☐
Ask your HCP about obtaining a pregnancy test before starting this protocol.☐
☐ Discuss radiation precautions with your health care providers to be started right after you receive radioactive iodine ablation on day _______.☐

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<td>1</td>
<td>Thyrogen 0.9 mg IM injection #1</td>
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| 2    | Thyrogen 0.9 mg IM injection #2  
This injection should follow 24 hours after the 1st Thyrogen injection |   | |
| 3    | Radioactive iodine ablation I-131 dose administered orally  
Radioiodine should follow 24 hours after the 2nd Thyrogen injection |   | |
| 4    |   |   | |
| 5    |   |   | |
| 6, 7, or 8+ | Post-therapy whole body scan  
(Your physician may decide that post-therapy scanning may be delayed additional days) |   | |

Your Thyrogen Diagnostic Testing Schedule and Checklist for Whole Body Scan and Thyroglobulin Testing (to be filled out by your doctor or nurse)

☐ You are having both a stimulated thyroglobulin (Tg) blood test and a whole body scan (WBS) with Thyrogen
☐ Follow a low-iodine diet before ablation therapy
☐ Start low-iodine diet on _______  ☐ End low-iodine diet on _______
☐ You will receive two Thyrogen injections. The dates, times and location for your appointments are listed on the schedule below.☐
Ask your HCP about obtaining a pregnancy test before starting this protocol.☐

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| 2    | Thyrogen 0.9 mg IM injection #2  
This injection should follow 24 hours after the 1st Thyrogen injection |   | |
| 3    | ☐ Radioactive iodine I-131 Scanning dose administered orally.  
Radioiodine should follow 24 hours after the 2nd Thyrogen injection |   | |
| 4    |   |   | |
| 5    | ☐ I-131 whole body scan  
☐ Thyroglobulin (Tg) blood test |   | |

Your Thyrogen Diagnostic Testing Schedule and Checklist for Stimulated Thyroglobulin Testing Only (to be filled out by your nurse or doctor)

☐ You are having only a stimulated thyroglobulin (Tg) blood test with Thyrogen
☐ You will receive two Thyrogen injections. The dates, times and location for your appointments are listed on the schedule below.

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This injection should follow 24 hours after the 1st Thyrogen injection |   | |
| 3    |   |   | |
| 4    |   |   | |
| 5    | ☐ Thyroglobulin (Tg) blood test |   | |
In order to ensure the safety of patients and families, the American Thyroid Association created recommendations for radiation safety. Talk to your doctor about specific restrictions or recommendations, and the length of time you should observe them based on your treatment.

Radioiodine is a radioactive substance that is commonly used in patients with well-differentiated thyroid cancer. The treatment dose of radioiodine swallowed will be absorbed through your gastrointestinal tract and will be taken up by any thyroid tissue that is present. Nearly all of the radioiodine will be eliminated from the body during the first week after treatment, primarily through urine. Small amounts will also be excreted in saliva, perspiration and feces.

Your doctor or member of the Radioiodine Treatment Team will discuss with you the following items and fill in the number of days related to each.

☐ Days that you need to stay >3 feet away from your adult family members and caregivers for at least 18 hours a day, and at least 6 feet away as much as possible.

☐ Days that you need to stay >6 feet away from babies, children younger than 16 years old and pregnant women.

☐ Days that you need to stay away from work and close contact with others in public places (movies, shopping, etc).

☐ Days that you need to stay away from school or day-care (includes both teachers and students).

Recommendations After Therapy

AT HOME

Ask your doctor for the number of days to:

☐ Sleep alone in a bed that is >6 feet away from another person, and, if possible, use a separate bedroom or sleeping room all by yourself;

☐ Not kiss anyone or engage in sexual activity;

☐ Move your bowels every day and use a laxative if you need help;

☐ Empty your bladder (urinate) every hour or so during the day of, and day after your radioiodine treatment; follow your doctor’s advice on how much fluid to drink;

☐ Use wipes (preferably flushable) to clean the toilet seat after use; men should sit down to urinate and use wipes to remove splatter of urine; wipe yourself dry after urinating so that you do not drip;

☐ For a phone you share with others, after use, wipe off the mouthpiece, or, while using, cover the phone with a plastic bag that, after use, is placed in specific plastic trash bag.

General Recommendations

(especially for patients sharing a bathroom)

☐ Flush the toilet after each time you use it; flush toilet paper and wipes;

☐ Always wash your hands well after using the toilet;

☐ Rinse the sink and wash your hands after brushing your teeth to wash away the saliva (spit);

☐ Do not share your toothbrush, razor, face cloth, towel, food or drinks, spoons, forks, glasses and dishes;

☐ Shower every day for at least the first 2 days after your treatment;

☐ Do not cook for other people. If cooking is necessary, use plastic gloves and dispose of in the specified plastic trash bag;

☐ Wash your dishes in a dishwasher or by hand; it is better not to use disposable (throw away) dishes which must be put into a specified plastic trash bag;

☐ Try to flush any tissues or any other items that contain anything from your body, such as blood, down the toilet; items that cannot be flushed, such as menstrual pads, bandages, paper/plastic dishes, spoons and forks and paper towels should be put in the specified plastic trash bag;

☐ Wash your underwear, pajamas, sheets, towels and any clothes that contain sweat, blood or urine by themselves; use a standard washing machine; you do not need to use bleach and do not need extra rinses;

☐ Have any one who helps you clean up vomit, blood, urine, or stool wear plastic gloves; the gloves should then be put in the specified trash plastic bag.
Post-treatment Information for Radioiodine Therapy

Trash Recommendations

- Keep the specified plastic trash bags separate from other trash; keep the bags away from children and animals;
- A member of your Radioiodine Treatment Team will tell you how and when to get rid of the specified plastic trash bag; you may be asked to bring the bag back to your treatment facility, or, after 80 days, the bag may be removed with other household trash.

Pets

- Usually pets will not receive enough radiation exposure to harm them. But do not sleep or come in close contact with pets (ask your doctor for how long) since your saliva, perspiration or other secretions may be carried away by the pet and transferred to other people.

OUTSIDE THE HOME

Ask Your Doctor or a member of the Radioiodine Treatment Team when:

- It will be safe to eat out, go shopping and attend events such as religious services, parties and movies;
- You will be able to return to work and to care for or teach others;
- It would be safe to donate blood;
- Special or longer distance travel is possible (Note: For up to 3 months or more following radioiodine treatment you may set off radiation detectors at: national borders, airports, bus and train stations, tunnels, bridges, trash collection sites and even your place of employment); a member of your Radioiodine Treatment Team will issue you a letter or card describing the therapy and the phone number of a person knowledgeable about your treatment (usually at the treating facility) in case local law enforcement agents need to check on this information; you should keep the letter or card containing the information with you whenever you are traveling for at least 3 months.

Emergency Care

- You will get an information card or letter at the time of your treatment that will show the date, type and amount of radioiodine that you were treated with; carry this card with you at all times for at least 3 months following your treatment;
- If you are in a traffic accident or any other medical emergency during the first week after your treatment, you should show this card to the medical people to let them know about the date and dose of your radioiodine treatment.

IMPORTANT INFORMATION FOR PATIENTS: RISKS OF RADIATION

Radiation exposure to others should always be As Low As Reasonably Achievable, a goal often abbreviated as ALARA. If you follow the above advice, the radiation from you to others is likely to be less than what they receive from radiation in nature over a year’s time.

Contact your doctor if you have any questions, and particularly if any of the above instructions cannot be followed and/or if you see anything that may have accidentally or unavoidably increased exposure of others to radiation.

ThyrogenONE is the primary resource for financial assistance for THYROGEN. Contact a dedicated case manager at ThyrogenONE at 1-88-THYROGEN (1-888-497-6436).

Do you have private health insurance?
This may be insurance that you receive through your employer (non-government) or you get yourself. The Thyrogen Co-Pay Assistance Program can help with the cost of THYROGEN. Eligible patients qualify for a maximum annual co-pay assistance amount of $1,000.

For questions about eligibility or program benefits, please call your ThyrogenONE case manager at 1-88-THYROGEN (1-888-497-6436).

Are you uninsured?
If THYROGEN has been prescribed by your physician based on medical need, and you are uninsured or have a plan that does not cover THYROGEN, then we may be able to provide THYROGEN, free of charge, through our Patient Assistance Program.

To learn more, or determine if you might qualify for assistance, contact your doctor’s office.

Note: Sanofi Genzyme’s Patient Assistance Program may be discontinued at any time at the discretion of the Patient Assistance Program Committee.

ThyrogenONE is available to answer any questions you have. You can contact your ThyrogenONE case manager at 1.88.THYROGEN (1.888.497.6436)

Learn more at www.THYROGEN.com

PLEASE SEE ACCOMPANYING FULL PRESCRIBING INFORMATION
Preparing for Scans with a Low-Iodine Diet

Before undergoing radioactive scanning, you may be asked by your physician to follow a low-iodine diet. The following diet tips and sample menus may help you manage your low-iodine diet. Of course, as with other aspects of your therapy, it’s important to consult with your healthcare provider about diet changes and other test preparation.

A low-iodine diet does not restrict sodium or salt. It only restricts iodized salt or sea salt. Any salt that is labeled non-iodized may be used freely.

**Foods you can eat**
- Kosher salt
- Egg whites
- Fresh non-cured meat from the butcher
- Fresh fruits and vegetables, washed well (limit bananas, spinach, and broccoli)
- Frozen vegetables with no added salt
- Canned peaches, pears and pineapples
- Matza/ Matzah/ Matzo Homemade bread made from non-iodized salt and oil (not soy) instead of butter or milk
- Natural unsalted peanut butter
- Clear sodas
- Coffee or tea made with distilled water (with non-dairy creamer only)
- Popcorn popped in vegetable oil or air popped, with non-iodized salt
- Sorbet (without FD&C red dye #3)

**Foods to avoid that contain iodine**
- Iodized salt and sea salt
- All dairy products (milk, sour cream, cheese, cream, yogurt, butter, ice cream)
- Margarine
- Egg yolks
- Seafood (fish, shellfish, seaweed, kelp)
- Foods that contain carrageen, agar-agar, align, or alginate (all of these are made from seaweed)
- Cured and corned foods (ham, bacon, sausage, corned beef, tuna, etc.)
- Marinated chicken or turkey
- Dried fruit
- Canned vegetables
- Bread products that contain iodate dough conditioners
- Chocolate
- Molasses
- Soy products (soy sauce, soy milk, tofu)
- Foods that contain FD&C Red Dye #3

Please note
A low-iodine diet does not restrict sodium or salt. It only restricts iodized salt or sea salt. Any salt that is labeled non-iodized may be used freely.
Menu Suggestions

The sample menus below are examples of meals that are suitable as part of a low-iodine diet

### BREAKFAST
Sample Menu

- ¼ cup quick-cooking oatmeal, ½ cup water or apple juice, 2 tsp. honey, and 2 tbsp. raisins (optional)
- 1 medium banana, apple, or pear
- 8 oz. (1 cup) orange, grape, or grapefruit juice (fresh or reconstituted with distilled water)
- 1 cup coffee or tea, with 2 tsp. sugar (optional) and 1 tsp. powdered non-dairy creamer (optional)
- 12 oz. (1 ½ cup) distilled water

### LUNCH
Sample Menu

- 1 roasted chicken breast (meat only) seasoned with black pepper, non-iodized salt, and fresh herbs
- 1 small garden salad seasoned with olive oil and lemon juice to taste
- 1 medium orange, apple, or plum
- 1 cup coffee or tea, with 2 tsp. sugar (optional) and 1 tsp. powdered non-dairy creamer (optional)
- 12 oz. (1 ½ cup) distilled water

### DINNER
Sample Menu

- 6 oz. fresh chicken, beef, or turkey breast, may use black pepper, fresh or dried herbs, vegetable oil to season
- 1 baked or mashed potato without skin
- 1 cup fresh vegetables (examples: green beans, carrots)
- 1 cup jello made with water (any color but red) or sorbet
- 12 oz. (1 ½ cup) distilled water

### More Low-Iodine Diet Tips

- When you are maintaining your diet, it would be wise to avoid restaurant food, as it is difficult to determine the exact ingredients being used to prepare the food.
- You may want to shop and freeze or store your ingredients before starting your diet to avoid being tempted by iodine-containing foods at the store.

References

- The Light of Life Foundation, Inc. (2014). The Light of Life Foundation Cookbook (2nd ed.). Accessed online at lightoflifefoundation.org March 2020
THYROGEN® (thyrotropin alfa) for injection, for intramuscular use

Initial U.S. Approval: 1998

INDICATIONS AND USAGE

THYROGEN® is a thyroid stimulating hormone indicated for:

- **Adjunctive Diagnostic Tool for Well-Differentiated Thyroid Cancer:** Use as an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radioiodine imaging in the follow-up of patients with well-differentiated thyroid cancer who have previously undergone thyroidectomy. (1.1)

  **Limitations of Use:**
  - THYROGEN-stimulated Tg levels are generally lower than, and do not correlate with Tg levels after thyroid hormone withdrawal.
  - Even when THYROGEN-Tg testing is performed in combination with radioiodine imaging, there remains a risk of missing a diagnosis of thyroid cancer or underestimating the extent of the disease.
  - Anti-Tg Antibodies may confound the Tg assay and render Tg levels uninterpretable.

- **Adjunct for Thyroid Remnant Ablation in Well-Differentiated Thyroid Cancer:** Use as an adjunctive treatment for radioiodine ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy. (1.2)

  **Limitations of Use:**
  - The effect of THYROGEN on thyroid cancer recurrence greater than 5 years post-remnant ablation has not been evaluated.

Dosage Forms and Strengths

For injection: 0.9 mg of thyrotropin alfa as a lyophilized powder in a single-dose vial (3)

CONTRAINDICATIONS

- If THYROGEN is administered with radioiodine, the contraindications to radioiodine also apply to this combination regimen. (4)

WARNINGS AND PRECAUTIONS

- THYROGEN-induced hyperthyroidism: Hospitalization for administration of THYROGEN and postadministrative observation should be considered for patients at risk. (5.1)
- Stroke: Stroke in female patients as well as other neurologic events in patients with central nervous system metastases. (5.2, 5.3)
- Sudden rapid tumor enlargement: Sudden, rapid and painful enlargement in distant metastatic thyroid cancer. (5.3)
- Risks associated with radioiodine (RAI) combination treatment: If THYROGEN is administered with RAI, the warnings and precautions for RAI also apply to this combination regimen. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (>5%) reported in clinical trials were nausea and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Concomitant use of THYROGEN and radioiodine (RAI) is contraindicated in pregnancy. (4, 8.1)
- Lactation: Concomitant use of THYROGEN and therapeutic RAI is contraindicated in lactating women. (4, 8.2)
- Renal Impairment: Elimination of THYROGEN is significantly slower in dialysis-dependent end-stage renal disease patients, resulting in prolonged elevation of TSH levels. (8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Adjunctive Diagnostic Tool for Well-Differentiated Thyroid Cancer

THYROGEN® is indicated for use as an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radioiodine imaging in the follow-up of patients with well-differentiated thyroid cancer who have previously undergone thyroidectomy.

Limitations of Use:

- THYROGEN-stimulated Tg levels are generally lower than, and do not correlate with, Tg levels after thyroid hormone withdrawal [see Clinical Studies (14.1)].
- Even when THYROGEN-stimulated Tg testing is performed in combination with radioiodine imaging, there remains a risk of missing a diagnosis of thyroid cancer or of underestimating the extent of disease.
- Anti-Tg antibodies may confound the Tg assay and render Tg levels uninterpretable [see Clinical Studies (14.1)]. Therefore, in such cases, even with a negative or low-stage THYROGEN radioiodine scan, consideration should be given to further evaluating patients.

1.2 Adjunct for Thyroid Remnant Ablation in Well-Differentiated Thyroid Cancer

THYROGEN is indicated for use as an adjunctive treatment for radioiodine ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of distant metastatic thyroid cancer.

Limitations of Use:

- The effect of THYROGEN on thyroid cancer recurrence greater than five years post-remnant ablation has not been evaluated [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

THYROGEN should be used by physicians knowledgeable in the management of patients with thyroid cancer.

THYROGEN is indicated as a two-injection regimen. The recommended dosage of THYROGEN is a 0.9 mg intramuscular injection to the buttock followed by a second 0.9 mg intramuscular injection to the buttock 24 hours later.

THYROGEN should be administered intramuscularly only. THYROGEN should not be administered intravenously.

Pretreatment with glucocorticoids should be considered for patients in whom tumor expansion may compromise vital anatomic structures [see Warnings and Precautions (5.3)].

Routine measurement of serum TSH levels is not recommended after THYROGEN use.

2.2 Reconstitution, Preparation, and Administration of THYROGEN
The supplied lyophilized powder must be reconstituted with Sterile Water for Injection, USP. THYROGEN should be prepared, and administered in the following manner:

- Reconstitute each 0.9 mg vial of THYROGEN with 1.2 mL of Sterile Water for Injection, USP to yield a single-dose solution containing 0.9 mg/mL of thyrotropin alfa that delivers 1 mL (0.9 mg).
- Gently swirl the contents of the vial until all the material is dissolved. Do not shake the solution.
- Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. The reconstituted THYROGEN solution should be clear and colorless. Do not use if the solution has particulate matter or is cloudy or discolored.
- Withdraw 1 mL of the reconstituted THYROGEN solution (0.9 mg of thyrotropin alfa) and inject intramuscularly in the buttocks. Discard any unused portions.
- The reconstituted THYROGEN solution must be injected within 3 hours unless refrigerated.
- If necessary, the reconstituted solution can be stored refrigerated at a temperature between 2°C and 8°C (36°F to 46°F) for up to 24 hours, while avoiding microbial contamination.
- Do not mix with other substances.

2.3 Timing of Serum Thyroglobulin Testing Following THYROGEN Administration

For serum thyroglobulin testing, the serum sample should be obtained 72 hours after the final injection of THYROGEN [see Clinical Studies (14.1)].

2.4 Timing for Remnant Ablation and Diagnostic Scanning Following THYROGEN Administration

Oral radioiodine should be given 24 hours after the second injection of THYROGEN in both remnant ablation and diagnostic scanning. The activity of $^{131}$I is carefully selected at the discretion of the nuclear medicine physician.

Diagnostic scanning should be performed 48 hours after the radioiodine administration.

3 DOSAGE FORMS AND STRENGTHS

For injection: 0.9 mg white to off-white lyophilized powder in a single-dose vial

4 CONTRAINDICATIONS

If THYROGEN is administered with radioiodine, the contraindications to radioiodine also apply to this combination regimen. Refer to the radioiodine prescribing information for a list of contraindications for radioiodine.

5 WARNINGS AND PRECAUTIONS

5.1 THYROGEN-Induced Hyperthyroidism
When given to patients who have substantial thyroid tissue still in situ or functional thyroid cancer metastases, THYROGEN is known to cause a transient (over 7 to 14 days) but significant rise in serum thyroid hormone concentration. There have been reports of death in non-thyroidectomized patients and in patients with distant metastatic thyroid cancer in which events leading to death occurred within 24 hours after administration of THYROGEN. Patients with residual thyroid tissue at risk for THYROGEN-induced hyperthyroidism include the elderly and those with a known history of heart disease. Hospitalization for administration of THYROGEN and postadministration observation in patients at risk should be considered.

5.2 Stroke

There are postmarketing reports of radiologically-confirmed stroke and neurological findings suggestive of stroke unconfirmed radiologically (e.g., unilateral weakness) occurring within 72 hours (range 20 minutes to three days) of THYROGEN administration in patients without known central nervous system metastases. The majority of such patients were young women taking oral contraceptives at the time of their event or had other risk factors for stroke, such as smoking or a history of migraine headaches. The relationship between THYROGEN administration and stroke is unknown. Patients should be well-hydrated prior to treatment with THYROGEN.

5.3 Sudden Rapid Tumor Enlargement

Sudden, rapid and painful enlargement of residual thyroid tissue or distant metastases can occur following treatment with THYROGEN. This may lead to acute symptoms, which depend on the anatomical location of the tissue. Such symptoms include acute hemiplegia, hemiparesis, and loss of vision one to three days after THYROGEN administration. Laryngeal edema, pain at the site of distant metastasis, and respiratory distress requiring tracheotomy have also been reported after THYROGEN administration.

Pretreatment with glucocorticoids should be considered for patients in whom tumor expansion may compromise vital anatomic structures.

5.4 Risks Associated with Radioiodine Treatment

If THYROGEN is administered with radioiodine (RAI), the warnings and precautions for RAI, apply to this combination regimen. Refer to the RAI prescribing information for a full list of the warnings and precautions for RAI.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to THYROGEN in 481 thyroid cancer patients who participated in a total of 6 clinical trials of THYROGEN: 4 trials for diagnostic use and 2 trials for ablation. In clinical trials, patients had undergone near-total thyroidectomy and had a mean age of 46.1 years. Thyroid cancer diagnosis was as follows: papillary (69.2%), follicular (12.9%), Hurthle cell (2.3%) and papillary/follicular (15.6%). Most patients received 2 intramuscular injections of 0.9 mg of THYROGEN injection gin 24 hours apart [see Clinical Studies (14.1, 14.2)].
The safety profile of patients who have undergone thyroidectomy and received THYROGEN as adjunctive treatment for radioiodine ablation of thyroid tissue remnants for well-differentiated thyroid cancer did not differ from that of patients who received THYROGEN for diagnostic purposes.

Reactions reported in ≥1% of patients in the combined trials are summarized in Table 1. In some studies, an individual patient may have participated in both THYROGEN and thyroid hormone withdrawal [see Clinical Studies (14.1, 14.2)].

Table 1: Summary of Adverse Reactions by THYROGEN and Thyroid Hormone Withdrawal in Pooled Clinical Trials (≥1% of Patients in any Phase)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>THYROGEN (N=481) n (%)</th>
<th>Thyroid Hormone Withdrawal (N=418) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>53 (11)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Headache</td>
<td>29 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (2)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of THYROGEN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Transient (<48 hours) influenza-like symptoms, including fever (>100°F/38°C), chills/shivering, myalgia/arthritis, fatigue/asthenia/malaise, headache, and chills.
- Hypersensitivity including urticaria, rash, pruritus, flushing, and respiratory signs and symptoms.
- Injection site reactions, including pain, erythema, bruising, and pruritus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

THYROGEN may be used in combination with radioiodine (RAI). If THYROGEN is administered with RAI, the combination regimen is contraindicated in pregnant women because fetal exposure to RAI can lead to neonatal hypothyroidism, which in some cases is severe and irreversible. Refer to the RAI prescribing information for more information on use during pregnancy.

Available data from case reports and postmarketing experience with THYROGEN use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects,
miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with THYROGEN.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

The concomitant use of THYROGEN and therapeutic radioiodine (RAI) is contraindicated in lactating women because RAI concentrates in the breast tissue and increases the risk of radiation breast toxicity (refer to the therapeutic RAI Prescribing Information).

If THYROGEN is administered with RAI for diagnostic use, discontinue breastfeeding after RAI administration because of the potential for serious adverse reactions from RAI in the breastfed infant (refer to the diagnostic RAI Prescribing Information).

If THYROGEN is not administered with RAI, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for THYROGEN and any potential adverse effects on the breastfed child from THYROGEN or from the underlying maternal condition.

There are no available data on the presence of thyrotropin alfa in human milk, the effects on the breastfed infant, or the effects on milk production.

8.3 Females and Males of Reproductive Potential

THYROGEN may be used in combination with radioiodine (RAI). If THYROGEN is administered with RAI, the information for RAI regarding pregnancy testing, contraception, and infertility also applies to the combination regimen. Refer to the RAI prescribing information for additional information.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In pooled clinical studies of THYROGEN, 60 patients (12%) were >65 years, and 421 (88%) were ≤65 years of age. Results from controlled trials do not indicate a difference in the safety and efficacy of THYROGEN between adult patients less than 65 years and those over 65 years of age [see Warnings and Precautions (5.1)].

8.6 Renal Impairment

Elimination of THYROGEN is significantly slower in dialysis-dependent end-stage renal disease (ESRD) patients, resulting in prolonged elevation of TSH levels.

10 OVERDOSAGE

In clinical trials of THYROGEN, three patients experienced symptoms after receiving THYROGEN doses higher than those recommended. Two patients had nausea after a 2.7 mg IM dose (3 times the recommended dose), and in one of these patients, the event was accompanied
by weakness, dizziness and headache. Another patient experienced nausea, vomiting and hot flashes after a 3.6 mg IM dose (4 times the recommended dose). There is no specific therapy for THYROGEN overdose. Supportive care is recommended.

11 DESCRIPTION

Thyrotropin alfa, a recombinant human thyroid stimulating hormone, is a heterodimeric glycoprotein comprised of two non-covalently linked subunits, an alpha subunit of 92 amino acid residues containing two N-linked glycosylation sites and a beta subunit of 118 residues containing one N-linked glycosylation site. The amino acid sequence of thyrotropin alfa is identical to that of human pituitary TSH. Thyrotropin alfa is synthesized in a genetically modified Chinese hamster ovary cell line.

Both thyrotropin alfa and naturally occurring human pituitary TSH are synthesized as a mixture of glycosylation variants. Unlike pituitary TSH, which is secreted as a mixture of sialylated and sulfated forms, thyrotropin alfa is sialylated but not sulfated. The biological activity of thyrotropin alfa is determined by a cell-based bioassay. In this assay, cells expressing a functional TSH receptor and a cAMP-responsive element coupled to a heterologous reporter gene, luciferase, enable the measurement of thyrotropin alfa activity by measuring the luciferase response. The specific activity of thyrotropin alfa is determined relative to an internal Genzyme reference standard that was calibrated against the World Health Organization (WHO) human TSH reference standard.

THYROGEN (thyrotropin alfa) for injection is a sterile, white to off-white lyophilized powder in a single-dose vial for intramuscular use after reconstitution.

Each single-dose vial provides 0.9 mg of thyrotropin alfa, and contains mannitol (36 mg); sodium chloride (2.4 mg); sodium phosphate dibasic, heptahydrate (3.7 mg); and sodium phosphate monobasic, monohydrate (1.4 mg). After reconstitution with 1.2 mL of Sterile Water for Injection, USP, the concentration is 0.9 mg/mL with a deliverable volume of 1 mL (0.9 mg) and a pH of approximately 6.5 to 7.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Thyrotropin (TSH) is a pituitary hormone that stimulates the thyroid gland to produce thyroid hormone. Binding of thyrotropin alfa to TSH receptors on normal thyroid epithelial cells or on well-differentiated thyroid cancer tissue stimulates iodine uptake and organification, and synthesis and secretion of thyroglobulin (Tg), triiodothyronine (T3) and thyroxine (T4).

The effect of thyroid stimulating hormone activation of thyroid cells is to increase uptake of radioiodine to allow scan detection or radioiodine killing of thyroid cells. TSH activation also leads to the release of thyroglobulin by thyroid cells. Thyroglobulin functions as a tumor marker which is detected in blood specimens.

12.3 Pharmacokinetics

The pharmacokinetics of THYROGEN was studied in 16 patients with well-differentiated thyroid cancer given a single 0.9 mg IM dose. Mean peak serum TSH concentrations of 116±38 mU/L were reached between 3 and 24 hours after injection (median of 10 hours). The mean apparent elimination half-life was 25±10 hours. The organ(s) of TSH clearance in man have not
been identified, but studies of pituitary-derived TSH suggest the involvement of the liver and kidneys.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term toxicity studies in animals have not been performed with THYROGEN to evaluate the carcinogenic potential of the drug. THYROGEN was not mutagenic in the bacterial reverse mutation assay. Studies have not been performed with THYROGEN to evaluate the effects on fertility.

14 CLINICAL STUDIES

14.1 Clinical Trials of THYROGEN as an Adjunctive Diagnostic Tool for Well-Differentiated Thyroid Cancer

Two prospective, randomized phase 3 clinical trials were conducted in patients with well-differentiated thyroid cancer to compare $^{131}$I whole body scans obtained after THYROGEN injection to $^{131}$I whole body scans after thyroid hormone withdrawal. A cross-over, non-blinded design was used in both trials. Oral radioiodine was given 24 hours after the second injection of THYROGEN, and scanning was done 48 hours after the radioiodine administration. Each patient was scanned first following THYROGEN and then scanned after thyroid hormone withdrawal. In both studies, the primary endpoint was the rate of concordant scans (scan findings in agreement in a given patient using each preparation method).

Study 1 (n=127) compared the diagnostic scanning following a THYROGEN regimen of 0.9 mg IM daily on two consecutive days to thyroid hormone withdrawal. In addition to body scans, Study 2 (n=229) also compared thyroglobulin (Tg) levels obtained after THYROGEN to those at baseline and to those after thyroid hormone withdrawal. All Tg testing was performed in a central laboratory using a radioimmunoassay (RIA) with a functional sensitivity of 2.5 ng/mL. Patients who were included in the Tg analysis were those who had undergone total or near-total thyroidectomy with or without $^{131}$I ablation, had <1% uptake in the thyroid bed on a scan after thyroid hormone withdrawal, and did not have detectable anti-Tg antibodies. The maximum THYROGEN Tg value was obtained 72 hours after the final THYROGEN injection, and this value was used in the analysis.

Diagnostic Radioiodine Whole Body Scan Results

Study 1 enrolled 127 patients, 71% were female and 29% male, and mean age was 44 years. The study included the following forms of differentiated thyroid cancer: papillary cancer (88%), follicular cancer (9%), and Hurthle cell (2%). Study results are displayed in Table 2.

In Study 2, patients with differentiated thyroid cancer who had been thyroidectomized (n=229) were randomized into one of two THYROGEN treatment regimens: THYROGEN 0.9 mg IM daily on two consecutive days (n=117), and THYROGEN 0.9 mg IM daily on days 1, 4 and 7 (n=112). Each patient was scanned first using THYROGEN, then scanned using thyroid hormone withdrawal. The group receiving the THYROGEN 0.9 mg IM x 2 regimen was 63% female/27% male, had a mean age of 44 years, and generally had low-stage papillary or follicular cancer (AJCC/TNM Stage I 61%, Stage II 19%, Stage III 14%, Stage IV 5%). The group receiving the THYROGEN 0.9 mg IM x 3 regimen was 66% female/34% male, had a mean age
of 50 years, and generally had low-stage papillary or follicular cancer (AJCC/TNM Stage I 50%, Stage II 20%, Stage III 20%, Stage IV 9%). The amount of radioiodine used for scanning was 4 mCi ± 10%, and scanning times were lengthened in some patients to capture adequate images (30 minute scans, or 140,000 counts). Scan pairs were assessed by blinded readers. Study results are presented in Table 2.

**Table 2: Concordance of Positive Thyroid Scans Following THYROGEN Treatment with Scans Following Thyroid Hormone Withdrawal**

<table>
<thead>
<tr>
<th></th>
<th>Number of scan pairs by disease category</th>
<th>Concordance of scan pairs between THYROGEN scan and thyroid hormone withdrawal scan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1 (0.9 mg IM qd × 2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive for remnant or cancer in thyroid bed</td>
<td>48</td>
<td>81%</td>
</tr>
<tr>
<td>Positive for metastatic disease</td>
<td>15</td>
<td>73%</td>
</tr>
<tr>
<td>Total positive withdrawal scansa,b</td>
<td>63</td>
<td>79%</td>
</tr>
<tr>
<td><strong>Study 2 (0.9 mg IM qd × 2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive for remnant or cancer in thyroid bed</td>
<td>35</td>
<td>86%</td>
</tr>
<tr>
<td>Positive for metastatic Disease</td>
<td>9</td>
<td>67%</td>
</tr>
<tr>
<td>Total positive withdrawal scansa,b</td>
<td>44</td>
<td>82%</td>
</tr>
</tbody>
</table>

*a* Across both studies uptake was detected on the THYROGEN scan but not observed on the scan after thyroid hormone withdrawal in 5 patients with remnant or cancer in the thyroid bed.

*b* In the two clinical studies radioiodine scan results using thyroid hormone withdrawal were taken as the true clinical status of each patient and as the comparator for THYROGEN scans. Thyroid hormone withdrawal trace-positive scans were scored conservatively as positive with no allowance for false positives.

Across the two clinical studies, and scoring all false positives in favor of thyroid hormone withdrawal, the majority of positive scans using THYROGEN and thyroid hormone withdrawal were concordant. The THYROGEN scan failed to detect remnant and/or cancer localized to the thyroid bed in 17% (14/83) 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 29% (7/24) of patients in whom it was detected by a scan after thyroid hormone withdrawal.

**Thyroglobulin (Tg) Results**

THYROGEN Tg testing alone and in combination with diagnostic whole body scanning: comparison with results after thyroid hormone withdrawal

In anti-Tg antibody negative patients with a thyroid remnant or cancer (as defined by a withdrawal Tg ≥2.5 ng/mL or a positive scan [after thyroid hormone withdrawal or after radioiodine therapy]), the THYROGEN Tg was positive (≥2.5 ng/mL) in 69% (40/58) of patients after 2 doses of THYROGEN.

In these same patients, adding the whole body scan increased the detection rate of thyroid remnant or cancer to 84% (49/58) of patients after 2 doses of THYROGEN.
Among patients with metastatic disease confirmed by a post-treatment scan or by lymph node biopsy (35 patients), THYROGEN Tg was positive (≥2.5 ng/mL) in all 35 patients, while Tg on thyroid hormone suppressive therapy was positive (≥2.5 ng/mL) in 79% of these patients.

As with thyroid hormone withdrawal, the intra-patient reproducibility of THYROGEN testing with regard to both Tg stimulation and radiiodine imaging has not been studied.

**Hypothyroid Signs and Symptoms**

THYROGEN administration was not associated with the signs and symptoms of hypothyroidism that accompanied thyroid hormone withdrawal as measured by the Billewicz scale. Statistically significant worsening in all signs and symptoms were observed during the hypothyroid phase (p<0.01) (Figure 1).

**Figure 1: Hypothyroid Symptom Assessment Billewicz Scale Diagnostic Indication 0.9 mg THYROGEN q 24 hours × 2 doses vs Thyroid Hormone Withdrawal Phase**

### 14.2 Clinical Trials of THYROGEN as an Adjunct for Thyroid Remnant Ablation in Well-Differentiated Thyroid Cancer

A randomized, prospective clinical trial compared the rates of thyroid remnant ablation achieved after preparation of patients with thyroid hormone withdrawal or THYROGEN. Patients (n=63) with low-risk, well-differentiated thyroid cancer who underwent near-total thyroidectomy were made euthyroid after surgery by receiving thyroid hormone replacement and were subsequently
randomized to a thyroid hormone withdrawal or THYROGEN. Patients in the THYROGEN group received THYROGEN 0.9 mg IM daily on 2 consecutive days and radiiodine 24 hours after the second dose of THYROGEN. Patients in the thyroid hormone withdrawal group had the thyroid replacement withheld until they became hypothyroid. Patients in both groups received 100 mCi $^{131}I \pm 10\%$ with the intent to ablate any thyroid remnant tissue. The primary endpoint of the study was the rate of successful ablation, and was assessed 8 months later by a THYROGEN-stimulated radioiodine scan. Patients were considered successfully ablated if there was no visible thyroid bed uptake on the scan, or if visible, uptake was less than 0.1%. Table 3 summarizes the results of this evaluation.

### Table 3: Remnant Ablation in Clinical Trial of Patients with Well-Differentiated Thyroid Cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Age (Yr)</th>
<th>Gender (F:M)</th>
<th>Cancer Type (Pap:Fol)</th>
<th>Ablation Criterion (Measure at 8 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Hormone Withdrawal</td>
<td>43</td>
<td>24:6</td>
<td>29:1</td>
<td>Thyroid Bed Activity &lt;0.1%</td>
</tr>
<tr>
<td>(N=28)</td>
<td></td>
<td></td>
<td></td>
<td>No Visible Thyroid Bed Activity$^b$</td>
</tr>
<tr>
<td>THYROGEN</td>
<td>44</td>
<td>26:7</td>
<td>30:3</td>
<td>28/28 (100%)</td>
</tr>
<tr>
<td>(N=32)</td>
<td></td>
<td></td>
<td></td>
<td>24/28 (86%)</td>
</tr>
</tbody>
</table>

$^a$ 60 per protocol patients with interpretable scan data.

95% CI for difference in ablation rates THYROGEN minus Thyroid Hormone Withdrawal, = 7% to 27%.

$^b$ Interpretation by 2 of 3 reviewers.

95% CI for difference in ablation rates, THYROGEN minus Thyroid Hormone Withdrawal, = -31% to 9%.

Abbreviations: fol = follicular, pap = papillary

The mean radiation dose to blood was $0.266 \pm 0.061$ mGy/MBq in the THYROGEN group and $0.395 \pm 0.135$ mGy/MBq in the thyroid hormone withdrawal group. Radioiodine residence time in remnant tissue was $0.9 \pm 1.3$ hours in the THYROGEN group and $1.4 \pm 1.5$ hours in the thyroid hormone withdrawal group. It is not known whether this difference in radiation exposure would convey a clinical benefit.

Patients who completed were followed up for a median duration of 3.7 years (range 3.4 to 4.4 years) following radioiodine ablation. Tg testing was also performed. The main objective of the follow-up study was to evaluate the status of thyroid remnant ablation by using THYROGEN-stimulated neck imaging. Of the fifty-one patients enrolled, forty-eight patients received THYROGEN for remnant neck/whole body imaging and/or thyroglobulin testing. Only 43 patients had imaging. Patients were still considered to be successfully ablated if there was no visible thyroid bed uptake on the scan, or if visible, uptake was less than 0.1%. All patients from both original treatment groups who had scanning were found to still be ablated. Of 37 patients who were Tg-antibody negative, 16/17 (94%) of patients in the former thyroid hormone withdrawal group and 19/20 (95%) of patients in the former THYROGEN group maintained successful ablation measured as stimulated serum Tg levels of <2 ng/mL.

No patient had a definitive cancer recurrence during the 3.7 years of follow-up. Overall, 48/51 patients (94%) had no evidence of cancer recurrence, 1 patient had possible cancer recurrence
(although it was not clear whether this patient had a true recurrence or persistent tumor from the regional disease noted at the start of the initial study), and 2 patients could not be assessed.

Two large prospective multicenter randomized studies compared THYROGEN to thyroid hormone withdrawal using two different doses of radioactive iodine in patients with differentiated thyroid cancer who had been thyroidectomized. In both studies, patients were randomized to 1 of 4 treatment groups: THYROGEN + 30 mCi $^{131}$I, THYROGEN + 100 mCi $^{131}$I, thyroid hormone withdrawal + 30 mCi $^{131}$I, or thyroid hormone withdrawal + 100 mCi $^{131}$I. Patients were assessed for efficacy (ablation success rates) at approximately 8 months.

The first study (Study A) randomized 438 patients (tumor stages T1-T3, Nx, N0 and N1, M0). Ablation success was defined as radioiodine uptake of <0.1% in the thyroid bed and stimulated thyroglobulin levels of <2.0 ng/mL. Results are summarized below (Table 4).

Table 4: Remnant Ablation Rates in Study A

<table>
<thead>
<tr>
<th></th>
<th>THYROGEN</th>
<th>Thyroid Hormone Withdrawal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose radioiodine</td>
<td>91/108</td>
<td>91/106</td>
<td>182/214</td>
</tr>
<tr>
<td></td>
<td>(84.3%)</td>
<td>(85.8%)</td>
<td>(85.0%)</td>
</tr>
<tr>
<td>High-dose Radioiodine</td>
<td>92/102</td>
<td>92/105</td>
<td>184/207</td>
</tr>
<tr>
<td></td>
<td>(90.2%)</td>
<td>(87.6%)</td>
<td>(88.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>183/210</td>
<td>183/211</td>
<td>366/421</td>
</tr>
<tr>
<td></td>
<td>(87.1%)</td>
<td>(86.7%)</td>
<td>(86.9%)</td>
</tr>
</tbody>
</table>

95% CI of difference in ablation rate (low dose minus high dose): -10.2% to 2.6%
95% CI of difference in ablation rate (THYROGEN - Thyroid Hormone Withdrawal): -6.0% to 6.8%

For Study A, 434 (99%) of the original 438 patients were followed up for disease recurrence. The median follow-up was 6.5 years (0.03 to 10.6 years).

The second study (Study B) randomized 752 patients with low-risk thyroid cancer (tumor stages pT1 <1 cm and N1 or Nx, pT1 >1-2 cm and any N stage, or pT2 N0, all patients M0). Ablation success was defined by neck ultrasound and stimulated thyroglobulin of ≤1.0 ng/mL. Results are summarized below (Table 5).

Table 5: Remnant Ablation Rates in Study B

<table>
<thead>
<tr>
<th></th>
<th>THYROGEN</th>
<th>Thyroid Hormone Withdrawal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose radioiodine</td>
<td>160/177</td>
<td>156/170</td>
<td>316/347</td>
</tr>
<tr>
<td></td>
<td>(90.4%)</td>
<td>(91.8%)</td>
<td>(91.1%)</td>
</tr>
<tr>
<td>High-dose radioiodine</td>
<td>159/171</td>
<td>156/166</td>
<td>315/337</td>
</tr>
<tr>
<td></td>
<td>(93.0%)</td>
<td>(94.0%)</td>
<td>(93.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>319/348</td>
<td>312/336</td>
<td>631/684</td>
</tr>
<tr>
<td></td>
<td>(91.6%)</td>
<td>(92.9%)</td>
<td>(92.3%)</td>
</tr>
</tbody>
</table>

95% CI of difference in ablation rate (low dose minus high dose): -5.8% to 0.9%
95% CI of difference in ablation rate (THYROGEN minus Thyroid Hormone Withdrawal): -4.5% to 2.2%

For Study B, 726 (97%) of the original 752 patients were followed up for disease recurrence. The median follow-up was 5.4 years (0.5 to 9.2 years).
Five year follow-up data of THYROGEN for remnant ablation with two different RAI doses in Study A and Study B observed similar rates of thyroid cancer recurrence as thyroid hormone withdrawal.

14.3 Quality of Life

Quality of Life (QOL) was measured during both the diagnostic study [see Clinical Studies (14.1)] and the ablation of thyroid remnant study [see Clinical Studies (14.2)] using the SF-36 Health Survey, a standardized, patient-administered instrument assessing QOL across eight domains measuring both physical and mental functioning. In the diagnostic study and in the remnant ablation study, following THYROGEN administration, little change from baseline was observed in any of the eight QOL domains of the SF-36. Following thyroid hormone withdrawal in the diagnostic study, statistically significant negative changes were noted in all eight QOL domains of the SF-36. The difference between treatment groups was statistically significant (p<0.0001) for all eight QOL domains, favoring THYROGEN over thyroid hormone withdrawal (Figure 2). In the remnant ablation study, following thyroid hormone withdrawal, statistically significant negative changes were noted in five of the eight QOL domains (physical functioning, role physical, vitality, social functioning and mental health).

Figure 2: SF-36 Health Survey Results Quality of Life Domains Diagnostic Indication

16 HOW SUPPLIED/STORAGE AND HANDLING
THYROGEN (thyrotropin alfa) for injection is as a sterile white to off-white lyophilized powder in a single-dose vial. Each carton (NDC 58468-0030-2) contains two 0.9 mg single-dose vials of THYROGEN (NDC 58468-0030-1).

Store THYROGEN refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

17 PATIENT COUNSELING INFORMATION

Adverse Reactions

- Inform patients that the most common adverse events from clinical experience were nausea and headache.
- Advise patients to seek immediate medical attention should they experience severe symptoms.

Important Information

- Prior to THYROGEN administration, counsel patients to seek care immediately for any neurologic symptoms occurring after administration of the drug.
- Inform patients for whom THYROGEN induced hyperthyroidism could have serious consequences, hospitalization for administration of THYROGEN and postadministrative observation should be considered.

Dosing and Administration

- Patients should be instructed that THYROGEN is for intramuscular administration into the buttock only. THYROGEN should not be administered intravenously.
- Inform patients the treatment regimen is two doses of THYROGEN administered at a 24 hour interval.
- Encourage patients to remain hydrated prior to treatment with THYROGEN.

Schedule of Procedures

- Inform patients that if diagnostic scanning will be performed, radioiodine will be given 24 hours after the second injection of THYROGEN, and patients should return for the scan 48 hours after radioiodine administration.
- Inform patients that if serum Tg testing is performed, blood will be drawn 72 hours or later after the second injection of THYROGEN.
- Inform patients that if remnant ablation is performed radioiodine will be administered 24 hours after the second injection of THYROGEN.

Pregnancy and Lactation Risks Associated with Radioiodine Treatment

- When THYROGEN is administered in combination with radioiodine (RAI), refer to the RAI prescribing information for patient counseling information. Inform patients to notify their healthcare provider immediately in the event of a pregnancy [see Warnings and Precautions (5.4) and Use in Specific Populations (8.1, 8.3)].

Manufactured by:
Genzyme Corporation
Cambridge, MA 02142

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