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Thyrogen® (thyrotropin alfa for injection)

PROPOSED TEXT OF THE LABELING OF THE DRUG

1 **(Logo) Thyrogen**

2 **(thyrotropin alfa for injection)**

3 **DESCRIPTION**

4 Thyrogen® (thyrotropin alfa for injection) contains a highly purified recombinant form of
5 human thyroid stimulating hormone (TSH), a glycoprotein which is produced by
6 recombinant DNA technology. Thyrotropin alfa is synthesized in a genetically modified
7 Chinese hamster ovary cell line.

8 Thyrotropin alfa is a heterodimeric glycoprotein comprised of two non-covalently linked
9 subunits, an alpha subunit of 92 amino acid residues containing two N-linked
10 glycosylation sites and a beta subunit of 118 residues containing one N-linked
11 glycosylation site. The amino acid sequence of thyrotropin alfa is identical to that of
12 human pituitary thyroid stimulating hormone.

13 Both thyrotropin alfa and naturally occurring human pituitary thyroid stimulating
14 hormone are synthesized as a mixture of glycosylation variants. Unlike pituitary TSH,
15 which is secreted as a mixture of sialylated and sulfated forms, thyrotropin alfa is
16 sialylated but not sulfated. The biological activity of thyrotropin alfa is determined by a
17 cell-based bioassay. In this assay, cells expressing a functional TSH receptor and a
18 cAMP-responsive element coupled to a heterologous reporter gene, luciferase, enable the
19 measurement of rhTSH activity by measuring the luciferase response. The specific
20 activity of thyrotropin alfa is 4-12 IU/mg using this cell-based bioassay. The specific
21 activity of thyrotropin alfa is determined relative to an internal Genzyme reference
22 material that was calibrated against the World Health Organization (WHO) human
23 pituitary derived TSH reference standard NIBSC 84/703 using an *in vitro* bioassay that
24 measures the amount of cAMP produced by a bovine thyroid microsome preparation in
25 response to rhTSH. .

26 Thyrogen is supplied as a sterile, non-pyrogenic, white to off-white lyophilized product,
27 intended for intramuscular (IM) administration after reconstitution with Sterile Water for
28 Injection, USP. Each vial of Thyrogen contains 1.1 mg thyrotropin alfa (4-12IU/mg), 36
29 mg Mannitol, 5.1 mg Sodium Phosphate, and 2.4 mg Sodium Chloride.

30 After reconstitution with 1.2 mL of Sterile Water for Injection, USP, the thyrotropin alfa
31 concentration is 0.9 mg/mL. The pH of the reconstituted solution is approximately 7.0.

32 **CLINICAL PHARMACOLOGY**

33 **Pharmacodynamics**

34 Thyrotropin alfa (recombinant human thyroid stimulating hormone) is a heterodimeric
35 glycoprotein produced by recombinant DNA technology. It has comparable biochemical

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36 properties to the human pituitary TSH. Binding of thyrotropin alfa to TSH receptors on
37 normal thyroid epithelial cells or on well-differentiated thyroid cancer tissue stimulates
38 iodine uptake and organification, and synthesis and secretion of thyroglobulin (Tg),
39 triiodothyronine (T3) and thyroxine (T4).

40 In patients with thyroid cancer, a near total or total thyroidectomy is performed and
41 patients are placed on synthetic thyroid hormone supplements to replace endogenous
42 hormone and to suppress serum levels of TSH in order to avoid TSH-stimulated tumor
43 growth. Thereafter, patients are followed up for the presence of remnants or of residual
44 or recurrent cancer by thyroglobulin (Tg) testing while they remain on thyroid hormone
45 suppressive therapy and are euthyroid, or by Tg testing and radioiodine imaging after
46 thyroid hormone withdrawal. Thyrogen is an exogenous source of human TSH that offers
47 an additional diagnostic tool in the follow-up of patients with a history of well-
48 differentiated thyroid cancer.

49 **Pharmacokinetics**

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

56 **Clinical Trials**

57 Two phase 3 clinical trials were conducted in 358 evaluable patients with well-
58 differentiated thyroid cancer to compare 48-hour radioiodine (¹³¹I) whole body scans
59 obtained after Thyrogen to whole body scans after thyroid hormone withdrawal. One of
60 these trials also compared Tg levels obtained after Thyrogen to those on thyroid hormone
61 suppressive therapy, and to those after thyroid hormone withdrawal. All Tg testing was
62 performed in a central laboratory using a radioimmunoassay (RIA) with a functional
63 sensitivity of 2.5 ng/mL. Only successfully ablated patients (defined as patients who have
64 undergone total or near total thyroidectomy with or without radioiodine ablation, and with
65 < 1% uptake in the thyroid bed on a scan after thyroid hormone withdrawal) without
66 detectable anti-thyroglobulin antibodies were included in the Tg data analysis. The
67 maximum Thyrogen Tg value was obtained 72 hours after the final Thyrogen injection,
68 and this value was used in the analysis (see DOSAGE AND ADMINISTRATION).

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69 **Radioiodine Whole Body Scan Results**

70 The following table summarizes the scan data in patients with positive scans after
71 withdrawal of thyroid hormone from the phase 3 studies.

	# scan pairs by disease category	#(%) scan pairs in which Thyrogen scan <u>detected</u> disease seen on withdrawal scan	#(%) scan pairs in which Thyrogen scan <u>did not detect</u> disease seen on withdrawal scan
<u>First Phase 3 Study (0.9 mg IM qd x 2)</u>			
positive for remnant of cancer in thyroid bed	48	39(81)	9(19)
metastatic disease	15	11(73)	4(27)
total positive withdrawal scans*	63	50(79)	13(21)
<u>Second Phase 3 Study (0.9 mg IM qd x 2)</u>			
positive for remnant of cancer in thyroid bed	35	30(86)	5(14)
metastatic disease	9	6(67)	3(33)
total positive withdrawal scans*	44	36(82)	8(18)
<u>Second Phase 3 Study (0.9 mg IM q 72 hrs x 3)</u>			
positive for remnant of cancer in thyroid bed	41	35(85)	6(15)
metastatic disease	14	12(86)	2(14)
total positive withdrawal scans*	55	47(85)	8(15)

72 * Across all studies, uptake was detected on the Thyrogen scan but not observed on the scan after thyroid
73 hormone withdrawal in 5 patients with remnant or cancer in the thyroid bed.

74

75 **Across the two clinical studies, the Thyrogen scan failed to detect remnant and/or**
76 **cancer localized to the thyroid bed in 16% (20/124) of patients in whom it was**
77 **detected by a scan after thyroid hormone withdrawal. In addition, the Thyrogen**
78 **scan failed to detect metastatic disease in 24% (9/38) of patients in whom it was**
79 **detected by a scan after thyroid hormone withdrawal.**

80 **Thyroglobulin (Tg) Results:**

81 **Thyrogen Tg Testing Alone and in Combination with Radioiodine Imaging:**
82 **Comparison with Results after Thyroid Hormone Withdrawal:**

83 In Tg antibody negative patients with a thyroid remnant or cancer as defined by a
84 withdrawal Tg ≥ 2.5 ng/mL or a positive scan (after thyroid hormone withdrawal or after
85 radioiodine therapy), the Thyrogen Tg was ≥ 2.5 ng/mL in 69% (40/58) of patients after 2
86 doses of Thyrogen, and in 80% (53/66) of patients after 3 doses of Thyrogen. Across
87 both dosage groups, 45% had a Tg ≥ 2.5 ng/mL on thyroid hormone suppressive therapy.

88 In these same patients, adding the whole body scan increased the detection rate of thyroid

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89 remnant or cancer to 84% (49/58) of patients after 2 doses of Thyrogen and 94% (62/66)
90 of patients after 3 doses of Thyrogen.

91 **Thyrogen Tg Testing Alone and in Combination with Radioiodine Imaging**
92 **in Patients with Confirmed Metastatic Disease:**

93 Metastatic disease was confirmed by a post-treatment scan or by lymph node biopsy in 35
94 patients. Thyrogen Tg was ≥ 2.5 ng/mL in all 35 patients while Tg on thyroid hormone
95 suppressive therapy was ≥ 2.5 ng/mL in 79% of these patients.

96 In this same cohort of 35 patients with confirmed metastatic disease, the Thyrogen Tg
97 levels were below 10 ng/mL in 27 % (3/11) of patients after 2 doses of Thyrogen and in
98 13% (3/24) of patients after 3 doses of Thyrogen. The corresponding thyroid hormone
99 withdrawal Tg levels in these 6 patients were 15.6 – 137 ng/mL. The Thyrogen scan
100 detected metastatic disease in 1 of these 6 patients (see INDICATIONS AND USAGE,
101 Considerations in the Use of Thyrogen).

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

104 **Quality of Life:**

105 Following Thyrogen, no change was observed in any of the 8 domains of the SF-36
106 Health Survey, a patient-administered quality-of-life measurement instrument. Following
107 thyroid hormone withdrawal, statistically significant negative changes in quality of life
108 parameters were observed in 4 of the 8 SF-36 domains. These 4 domains were: physical
109 functioning, physical role, bodily pain and emotional role. No change was observed in
110 the following scales: general health, vitality, social functioning and mental health.

111 **Hypothyroid Signs and Symptoms:**

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

116 **UNABLE TO INSERT BAR GRAPH TITLED:**
117 **HYPOTHYROID SYMPTOM ASSESSMENT BILLEWICZ SCALE (0.9 mg**
118 **Thyrogen q24 x 2 doses)**

119 **INDICATIONS AND USAGE**

120 Thyrogen (thyrotropin alfa for injection) is indicated for use as an adjunctive diagnostic
121 tool for serum thyroglobulin (Tg) testing with or without radioiodine imaging in the
122 follow-up of patients with well-differentiated thyroid cancer.

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123 **Potential Clinical Uses:**

- 124 1. Thyrogen Tg testing may be used in patients with an undetectable Tg on thyroid
125 hormone suppressive therapy to exclude the diagnosis of residual or recurrent thyroid
126 cancer (see CLINICAL PHARMACOLOGY, Clinical Trials, Thyroglobulin (Tg)
127 Results).
- 128 2. Thyrogen testing may be used in patients requiring serum Tg testing and radioiodine
129 imaging who are unwilling to undergo thyroid hormone withdrawal testing and whose
130 treating physician believes that use of a less sensitive test is justified.
- 131 3. Thyrogen testing may be used in patients who are either unable to mount an adequate
132 endogenous TSH response to thyroid hormone withdrawal or in whom withdrawal is
133 medically contraindicated.

134 **Considerations in the Use of Thyrogen:**

- 135 **1. Even when Thyrogen-stimulated Tg testing is performed in combination with**
136 **radioiodine imaging, there remains a meaningful risk of missing a diagnosis of**
137 **thyroid cancer or of underestimating the extent of disease. Therefore, thyroid**
138 **hormone withdrawal Tg testing with radioiodine imaging remains the standard**
139 **diagnostic modality to assess the presence, location and extent of thyroid cancer.**
- 140 2. Thyrogen Tg levels are generally lower than, and do not correlate with Tg levels after
141 thyroid hormone withdrawal (see CLINICAL PHARMACOLOGY, Thyroglobulin
142 (Tg) Results).
- 143 3. A newly detectable Tg level or a Tg level rising over time after Thyrogen, or a high
144 index of suspicion of metastatic disease, even in the setting of a negative or low-stage
145 Thyrogen radioiodine scan, should prompt further evaluation such as thyroid hormone
146 withdrawal to definitively establish the location and extent of thyroid cancer. On the
147 other hand, none of the 31 patients studied with undetectable Thyrogen Tg levels
148 (< 2.5 ng/mL) had metastatic disease. Therefore, an undetectable Thyrogen Tg level
149 suggests the absence of clinically significant disease (see CLINICAL
150 PHARMACOLOGY, Clinical Trials).
- 151 4. The decisions whether to perform a Thyrogen radioiodine scan in conjunction with a
152 Thyrogen serum Tg test and whether and when to withdraw a patient from thyroid
153 hormone are complex. Pertinent factors in these decisions include the sensitivity of
154 the Tg assay used, the Thyrogen Tg level obtained, and the index of suspicion of
155 recurrent or persistent local or metastatic disease. In the clinical trials, combination
156 Tg and scan testing did enhance the diagnostic accuracy of Thyrogen in some cases
157 (see CLINICAL PHARMACOLOGY, Clinical Trials).
- 158 5. Thyrogen is not recommended to stimulate radioiodine uptake for the purposes of

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159 ablative radiotherapy of thyroid cancer.

160 6. The signs and symptoms of hypothyroidism which accompany thyroid hormone
161 withdrawal are avoided with Thyrogen (see CLINICAL PHARMACOLOGY, Clinical
162 Trials, Quality of Life, Hypothyroid Signs and Symptoms).

163 **PRECAUTIONS**

164 (see INDICATIONS AND USAGE, Considerations in the Use of Thyrogen)

165 **General**

166 The use of Thyrogen (thyrotropin alfa for injection) should be directed by physicians
167 knowledgeable in the management of patients with thyroid cancer.

168 **Thyroglobulin (Tg) antibodies may confound the Tg assay and render Tg levels**
169 **uninterpretable. Therefore, in such cases, even with a negative or low-stage**
170 **Thyrogen radioiodine scan, consideration should be given to evaluating patients**
171 **further with, for example, a confirmatory thyroid hormone withdrawal scan to**
172 **determine the location and extent of thyroid cancer.**

173 Thyrogen should be administered intramuscularly only. It should not be administered
174 intravenously.

175 TSH antibodies have not been reported in patients treated with Thyrogen in the clinical
176 trials, although only 27 patients received Thyrogen on more than one occasion.

177 Caution should be exercised when Thyrogen is administered to patients who have been
178 previously treated with bovine TSH and, in particular, to those patients who have
179 experienced hypersensitivity reactions to bovine TSH.

180 Thyrogen is known to cause a transient but significant rise in serum thyroid hormone
181 concentration. Therefore, caution should be exercised in patients with a known history of
182 heart disease and with significant residual thyroid tissue (see ADVERSE REACTIONS).

183 **Drug-Drug Interactions**

184 Formal interaction studies between Thyrogen and other medicinal products have not been
185 performed. In clinical trials, no interactions were observed between Thyrogen and the
186 thyroid hormones triiodothyronine (T3) and thyroxine (T4) when administered
187 concurrently.

188 The use of Thyrogen allows for radioiodine imaging while patients are euthyroid on
189 triiodothyronine (T3) and/or thyroxine (T4). Data on radioiodine ¹³¹I kinetics indicate that
190 the clearance of radioiodine is approximately 50% greater in euthyroid patients than in
191 hypothyroid patients, who have decreased renal function. Thus radioiodine retention is

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192 less in euthyroid patients at the time of imaging and this factor should be considered
193 when selecting the activity of radioiodine for use in radioiodine imaging.

194 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

199 **Pregnancy Category C**

200 Animal reproduction studies have not been conducted with Thyrogen.

201 It is also not known whether Thyrogen can cause fetal harm when administered to a
202 pregnant woman or can affect reproductive capacity. Thyrogen should be given to a
203 pregnant woman only if clearly needed.

204 **Nursing Mothers**

205 It is not known whether the drug is excreted in human milk. Because many drugs are
206 excreted in human milk, caution should be exercised when Thyrogen is administered to a
207 nursing woman.

208 **Pediatric Use**

209 Safety and effectiveness in pediatric patients below the age of 16 years have not been
210 established.

211 **Geriatric Use**

212 Results from controlled trials indicate no difference in the safety and efficacy of
213 Thyrogen between adult patients less than 65 years and those greater than 65 years of age.

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214 **ADVERSE REACTIONS**

215 Adverse reaction data are derived from the two clinical trials in which 381 patients were
216 treated with Thyrogen (thyrotropin alfa for injection) and from post-marketing
217 surveillance.

218 The most common adverse events (>5%) reported in clinical trials were: nausea (10.5%)
219 and headache (7.3%). Events reported in $\geq 1\%$ of patients in the trials are summarized in
220 the following table:

221 Summary of Adverse Events During Clinical Studies ($\geq 1\%$)

	% of Patients with Adverse Events (n) (n = 381)
<u>Body as a Whole</u>	
Headache	7.3%(28)
Asthenia	3.4%(13)
Chills	1.0%(4)
Fever	1.0%(4)
Flu Syndrome	1.0%(4)
<u>Digestive System</u>	
Nausea	10.5%(40)
Vomiting	2.1%(8)
Nausea and Vomiting	1.3%(5)
<u>Nervous System</u>	
Dizziness	1.6%(6)
Paresthesia	1.6%(6)

222

223 There have been several reports of hypersensitivity reactions including urticaria, rash,
224 pruritus, flushing and respiratory difficulties requiring treatment. However, in clinical
225 trials no patients have developed antibodies to thyrotropin alfa, either after single or
226 repeated (27 patients) use of the product.

227 Four patients out of 55 (7.3%) with CNS metastases who were followed in a special
228 treatment protocol experienced acute hemiplegia, hemiparesis or pain one to three days
229 after Thyrogen administration. The symptoms were attributed to local edema and/or focal
230 hemorrhage at the site of the cerebral or spinal cord metastases. In addition, one case
231 each of acute visual loss and of laryngeal edema with respiratory distress,, requiring
232 tracheotomy with onset of symptoms within 24 hours after Thyrogen administration, have
233 been reported in patients with metastases to the optic nerve and paratracheal areas,
234 respectively. In addition, sudden rapid and painful enlargement of locally recurring
235 papillary carcinoma has been reported with 12-48 hours of Thyrogen administration. The
236 enlargement was accompanied by dyspnea, stridor or dysphonia. Rapid clinical

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237 improvement occurred following glucocorticoid therapy. It is recommended that
238 pretreatment with glucocorticoid be considered for patients in whom local tumor
239 expansion may compromise vital anatomic structures.

240 A 77 year-old non-thyroidectomized patient with a history of heart disease and spinal
241 metastases who received 4 Thyrogen injections over 6 days in a special treatment protocol
242 experienced a fatal MI 24 hours after he received the last Thyrogen injection. The event
243 was likely related to Thyrogen-induced hyperthyroidism.

244 **OVERDOSAGE**

245 There has been no reported experience of overdose in humans. However, in clinical
246 trials, three patients experienced symptoms after receiving Thyrogen doses higher than
247 those recommended. Two patients had nausea after a 2.7 mg IM dose, and in one of these
248 patients, the event was accompanied by weakness, dizziness and headache. Another
249 patient experienced nausea, vomiting and hot flashes after a 3.6 mg IM dose.

250 In addition, one patient experienced symptoms after receiving Thyrogen intravenously.
251 This patient received 0.3 mg Thyrogen as a single intravenous bolus and, 15 minutes later
252 experienced severe nausea, vomiting, diaphoresis, hypotension (BP decreased from
253 115/66 mm Hg to 81/44 mm Hg) and tachycardia (pulse increased from 75 to 117 bpm).

254 **DOSAGE AND ADMINISTRATION**

255 Thyrogen 0.9 mg intramuscularly may be administered every 24 hours for two doses or
256 every 72 hours for three doses.

257 After reconstitution with 1.2 mL Sterile Water for Injection, a 1.0 mL solution (0.9 mg
258 thyrotropin alfa) is administered by intramuscular injection to the buttock.

259 For radioiodine imaging, radioiodine administration should be given 24 hours following
260 the final Thyrogen injection. Scanning should be performed 48 hours after radioiodine
261 administration (72 hours after the final injection of Thyrogen).

262 The following parameters utilized in the second Phase 3 study are recommended for
263 radioiodine scanning with Thyrogen:

- 264 • A diagnostic activity of 4 mCi (148 MBq) ¹³¹I should be used.
- 265 • Whole body images should be acquired for a minimum of 30 minutes and/or
266 should contain a minimum of 140,000 counts.
- 267 • Scanning times for single (spot) images of body regions should be 10-15 minutes
268 or less if the minimum number of counts is reached sooner (i.e. 60,000 for a large
269 field of view camera, 35,000 counts for a small field of view).

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270 For serum Tg testing, the serum sample should be obtained 72 hours after the final
271 injection of Thyrogen.

272 **INSTRUCTIONS FOR USE**

273 Thyrogen (thyrotropin alfa for injection) is for intramuscular injection to the buttock. The
274 powder should be reconstituted immediately prior to use with 1.2 mL of sterile Water for
275 Injection, USP. Each vial of Thyrogen and each vial of diluent, if provided, is intended
276 for single use. Discard unused portion of the diluent.

277 Thyrogen should be stored at 2-8°C (36-46°F). Each vial, after reconstitution with 1.2 mL
278 of the accompanying Sterile Water for Injection, USP, should be inspected visually for
279 particulate matter or discoloration before use. Any vials exhibiting particulate matter or
280 discoloration should not be used.

281 If necessary, the reconstituted solution can be stored for up to 24 hours at a temperature
282 between 2°C and 8°C, while avoiding microbial contamination.

283 DO NOT USE Thyrogen after the expiration date on the vial. Protect from light.

284 **HOW SUPPLIED**

285 Thyrogen (thyrotropin alfa for injection) is supplied as a sterile, non-pyrogenic,
286 lyophilized product. It is available either in a two-vial or a four-vial kit. The two-vial kit
287 contains two 1.1 mg vials of Thyrogen® (thyrotropin alfa for injection). The four-vial kit
288 contains two 1.1 mg vials of Thyrogen®, as well as two 10 mL vials of Sterile Water for
289 Injection, USP.

290 NDC 58468-1849-4 (4-vial-kit)

291 NDC 58468-0030-2 (2-vial-kit)

292 Store at 2-8°C.

293 **Rx ONLY**

294 Thyrogen® (thyrotropin alfa for injection)

295 **Genzyme Corporation**

296 **One Kendall Square**

297 **Cambridge, MA 02139**

298 **(800) 745-4447**