SAP / ID. number : PI THYROGEN-5 / XXXXXX		Film code : KSF/XXXXXX	
Country	: INDONESIA	Min. point size of text	: 6 pt
Version number	: 1	Type of text	: Ocean Sans Pro Family
Date	: 10.08.2023	Dimensions	: 190 x 300 mm
Material	: HVS 60 g/m²	Type of prefold	: 3x Horizontal - 1x Vertical
Pharmacode	: XXXXX	Dimension after folded	: 95 x 37.5 mm (± 2mm)
Prepared by	: Rahmat Hafid		

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Technical Information

outline

For Pharmacode

Thyrogen®

Thyrotropin alfa for injection

Lyophilized Powder for solution for injection

genzyme
A SANOFI COMPANY

sanofi

1. NAME OF THE MEDICINAL PRODUCT
Thyrogen 0.9 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial of Thyrogen contains a nominal value of 0.9 mg thyrotropin alfa. Following reconstitution, each vial of Thyrogen contains 0.9 mg of thyrotropin alfa in 1.0 mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Powder for solution for injection.
White to off-white lyophilized powder.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Thyrogen is indicated for use with serum thyroglobulin (Tg) testing with or without radioiodine imaging for the detection of thyroid remnants and well-differentiated thyroid cancer in post thyroidectomy patients maintained on hormone suppression therapy (THST).

Low risk patients with well-differentiated thyroid carcinoma who have undetectable serum Tg levels on THST and no rh (recombinant human) TSH-stimulated increase of Tg levels may be followed-up by assaying rh TSH-stimulated Tg levels.

Thyrogen is indicated for pre-therapeutic stimulation in combination with a range of 30 mCi (1.1 GBq) to 100 mCi (3.7 GBq) radioiodine for 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 (see section 4.4).

4.2 Posology and method of administration
Therapy should be supervised by physicians with expertise in thyroid cancer.

Posology
The recommended dose regimen is two doses of 0.9 mg thyrotropin alfa administered at a 24-hour interval by intramuscular injection only.

Paediatric population
Due to a lack of data on the use of Thyrogen in children, Thyrogen should be given to children only in exceptional circumstances.

Elderly population
Results from controlled trials indicate no difference in the safety and efficacy of Thyrogen between adult patients less than 65 years and those greater than 65 years of age, when Thyrogen is used for diagnostic purposes.

No dose adjustment is necessary in the elderly population (see section 4.4).

Renal/hepatic impairment
Information from post marketing surveillance, as well as published information, suggests that elimination of Thyrogen is significantly slower in dialysis-dependent end stage renal disease (ESRD) patients, resulting in prolonged elevation of TSH levels for several days after treatment. This may lead to increased risk of headache and nausea. There are no studies of alternative dose schedules of Thyrogen in patients with ESRD to guide dose reduction in this population.

In patients with significant renal impairment the activity of radioiodine should be carefully selected by the nuclear medicine physician.

The use of Thyrogen in patients with reduced liver function does not warrant special considerations.
Method of administration
After reconstitution with water for injection, 1.0 mL solution (0.9 mg thyrotropin alfa) is administered by intramuscular injection to the buttock. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

For radioiodine imaging or ablation, radioiodine administration should be given 24 hours following the final Thyrogen injection. Diagnostic scintigraphy should be performed 48 to 72 hours following radioiodine administration, whereas post-ablation scintigraphy may be delayed additional days to allow background activity to decline.

For diagnostic follow-up serum thyroglobulin (Tg) testing, the serum sample should be obtained 72 hours after the final injection of Thyrogen. Use of Thyrogen with Tg testing in follow up of post-thyroidectomy well differentiated thyroid cancer patients should be in accordance with official guidelines.

4.3 Contraindications
- Hypersensitivity to bovine or human thyroid stimulating hormone or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use
Thyrogen should not be administered intravenously.

When used as an alternative to thyroid hormone withdrawal, the combination of the whole body scintigraphy (WBS) and Tg testing after Thyrogen administration assures the highest sensitivity for detection of thyroid remnants or cancer. False negative results may occur with Thyrogen. If a high index of suspicion for metastatic disease persists, a confirmatory withdrawal WBS and Tg testing should be considered.

The presence of Tg autoantibodies can be expected in 18-40% of patients with differentiated thyroid cancer and may cause false negative serum Tg measurements. Therefore, both TgAb and Tg assays are needed.

Careful evaluation of benefit-risk relationships should be assessed for Thyrogen administration in high risk elderly patients who have heart disease (e.g. valvular heart disease, cardiomyopathy, coronary artery disease, and prior or current tachyarrhythmia including atrial fibrillation) and have not undergone thyroidectomy.

Thyrogen is known to cause a transient but significant rise in serum thyroid hormone concentration when given to patients who have substantial thyroid tissue still *in situ*. Therefore, careful evaluation of individual risk-benefit is necessary for patients with significant residual thyroid tissue.

Long term data in relation to use of the lower dose of radioiodine are not yet available.

Effect on tumour growth and/or size:
In patients with thyroid cancer, several cases of stimulated tumour growth have been reported during withdrawal of thyroid hormones for diagnostic procedures which have been attributed to the associated prolonged elevation of thyroid stimulating hormone (TSH) levels.
There is a theoretical possibility that Thyrogen, like thyroid hormone withdrawal, may lead to stimulated tumour growth. In clinical trials with thyrotropin alfa, which produces a short-term increase in serum TSH levels, no case of tumour growth has been reported.

Due to elevation of TSH levels after Thyrogen administration patients with metastatic thyroid cancer particularly in confined spaces such as the brain, spinal cord and orbit or disease infiltrating the neck, may experience local oedema or focal haemorrhage at the site of these metastases resulting in increased tumour size. This may lead to acute symptoms, which depend on the anatomical location of the tissue e.g. hemiplegia, hemiparesis, loss of vision have occurred in patients with CNS metastases. Laryngeal oedema, respiratory distress requiring tracheotomy, and pain at the site of metastasis have also been reported after Thyrogen administration. It is recommended that pre-treatment with corticosteroids be considered for patients in whom local tumour expansion may compromise vital anatomic structures.

Important information about some of the ingredients of Thyrogen
This medicinal product contains less than 1 mmol sodium (23 mg) per injection, i.e. essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction
Formal interaction studies between Thyrogen and other medicinal products have not been performed. In clinical trials, no interactions were observed between Thyrogen and the thyroid hormones triiodothyronine (T_3) and thyroxine (T_4) when administered concurrently.

The use of Thyrogen allows for radioiodine imaging while patients are euthyroid on thyroid hormone suppression treatment. Data on radioiodine kinetics indicate that the clearance of radioiodine is approximately 50% greater while euthyroid than during the hypothyroid state when renal function is decreased, thus resulting in less radioiodine retention in the body at the time of imaging. This factor should be considered when selecting the activity of radioiodine for use in radioiodine imaging.

4.6 Fertility, pregnancy and lactation
Pregnancy
Animal reproduction studies have not been conducted with Thyrogen.

It is not known whether Thyrogen can cause foetal harm when administered to a pregnant woman or whether Thyrogen can affect reproductive capacity.

Thyrogen in combination with diagnostic radioiodine whole body scintigraphy is contra-indicated in pregnancy (see section 4.3), because of the consequent exposure of the foetus to a high dose of radioactive material.

Breast-feeding
It is unknown whether thyrotropin alfa /metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Thyrogen should not be used during breast-feeding.

Fertility
It is not known whether Thyrogen can affect fertility in humans.

4.7 Effects on ability to drive and use machines
Thyrogen may reduce the ability to drive or use machines, since dizziness and headaches have been reported.

4.8 Undesirable effects
Summary of the safety profile
The most commonly reported adverse reactions are nausea and headache, occurring in approximately 11%, and 6% of patients, respectively.

Tabulated list of adverse reactions
The adverse reactions mentioned in the table, combine adverse reactions in the six prospective clinical trials (N=481) and undesirable effects that have been reported to Genzyme after licensure of Thyrogen.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The reporting rate is classified as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

	Very Common	Common	Uncommon	Not known
Infections and infestations			influenza	
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)				neoplasm swelling, metastatic pain
Nervous system disorders		dizziness, headache	ageusia, dysgeusia, paraesthesia	stroke, tremor
Cardiac disorders				palpitations
Vascular disorders				flushing
Respiratory, thoracic and mediastinal disorder				dyspnoea
Gastrointestinal disorders	nausea	vomiting	diarrhoea	
Skin and subcutaneous tissue disorders			urticaria, rash	pruritus, hyperhidrosis
Musculoskeletal and connective tissue disorder			neck pain, back pain	arthralgia, myalgia
General disorders and administration site conditions		fatigue, asthenia	influenza like illness, pyrexia, chills, feeling hot	discomfort, pain, pruritus, rash and urticaria at the site of injection
Investigations				TSH decreased

Description of selected adverse events
Very rare cases of hyperthyroidism or atrial fibrillation have been observed when Thyrogen 0.9 mg has been administered in patients with presence of either partial or entire thyroid gland.

Manifestations of hypersensitivity have been reported uncommonly in both clinical and post-marketing settings. These reactions consisted of urticaria, rash, pruritus, flushing and respiratory signs and symptoms.

In clinical trials involving 481 patients, no patients have developed antibodies to thyrotropin alfa either after single or repeated limited (27 patients) use of the product. The occurrence of antibodies which could interfere with endogenous TSH assays cannot be excluded.

Enlargement of residual thyroid tissue or metastases can occur following treatment with Thyrogen. This may lead to acute symptoms, which depend on the anatomical location of the tissue. For example, hemiplegia, hemiparesis or loss of vision have occurred in patients with CNS metastases. Laryngeal oedema, respiratory distress requiring tracheotomy, and pain at the site of metastasis have also been reported after Thyrogen administration. It is recommended that pretreatment with corticosteroids be considered for patients in whom local tumour expansion may compromise vital anatomic structures.

Very rare cases of stroke have been reported from world-wide post marketing experience in female patients. The relationship to Thyrogen administration is unknown.

4.9 Overdose
Data on exposure above the recommended dose is limited to clinical studies and a special treatment program. Three patients in clinical trials and one patient in the special treatment program experienced symptoms after receiving Thyrogen doses higher than those recommended. Two patients had nausea after 2.7 mg IM dose, and in one of these patients nausea was also accompanied by weakness, dizziness and headache. The third patient experienced nausea, vomiting and hot flushes after 3.6 mg IM dose. In the special treatment program, a 77 year-old patient with metastatic thyroid cancer who had not been thyroidectomised received 4 doses of Thyrogen 0.9 mg over 6 days, developed atrial fibrillation, cardiac decompensation and terminal myocardial infarction 2 days later.

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One additional patient enrolled in a clinical trial experienced symptoms after receiving Thyrogen intravenously. This patient received 0.3 mg of Thyrogen as a single intravenous (IV) bolus and, 15 minutes later experienced severe nausea, vomiting, diaphoresis, hypotension and tachycardia.

A suggested treatment in case of overdose would be the re-establishment of fluid balance and administration of an anti-emetic may also be considered.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Pituitary and Hypothalamic Hormones and Analogues, Anterior Pituitary Lobe Hormones and Analogues. ATC code for thyrotropin alfa: H01AB01

Mechanism of action
Thyrotropin alfa (recombinant human thyroid stimulating hormone) is a heterodimeric glycoprotein produced by recombinant DNA technology. It is comprised of two non-covalently linked subunits. The cDNAs encode for 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. It has comparable biochemical properties to natural human Thyroid Stimulating Hormone (TSH). Binding of thyrotropin alfa to TSH receptors on thyroid epithelial cells stimulates iodine uptake and organification, and synthesis and release of thyroglobulin, triiodothyronine (T3) and thyroxine (T4).

In patients with well-differentiated thyroid cancer, a near total or total thyroidectomy is performed. For optimal diagnosis of thyroid remnants or cancer via either radioiodine imaging or thyroglobulin testing and for radioiodine therapy of thyroid remnants, a high serum level of TSH is needed to stimulate either radioiodine uptake and/or thyroglobulin release. The standard approach to achieve elevated TSH levels has been to withdraw patients from thyroid hormone suppression therapy (THST), which usually causes patients to experience the signs and symptoms of hypothyroidism. With the use of Thyrogen, the TSH stimulation necessary for radioiodine uptake and thyroglobulin release is achieved while patients are maintained euthyroid on THST, thus avoiding the morbidity associated with hypothyroidism.

Clinical efficacy and safety
Diagnostic use
The efficacy and safety of Thyrogen for use with radioiodine imaging together with serum thyroglobulin testing for the diagnosis of thyroid remnants and cancer was demonstrated in two studies. In one of the studies, two dose regimens were examined: 0.9 mg intramuscular every 24 hours for two doses (0.9 mg x 2) and 0.9 mg intramuscular every 72 hours for three doses (0.9 mg x 3). Both dose regimens were effective and not statistically different from thyroid hormone withdrawal in stimulating radioiodine uptake for diagnostic imaging. Both dose regimens improved the sensitivity, accuracy and negative predictive value of Thyrogen-stimulated thyroglobulin alone or in combination with radioiodine imaging as compared to testing performed while patients remained on thyroid hormones.

In clinical trials, for the detection of thyroid remnants or cancer in ablated patients using a thyroglobulin assay with a lower limit of detection of 0.5 ng/mL, Thyrogen-stimulated thyroglobulin levels of 3 ng/mL, 2 ng/mL and 1 ng/mL corresponded with thyroglobulin levels after withdrawal of thyroid hormone of 10 ng/mL, 5 ng/mL and 2 ng/mL, respectively. In these studies the use of thyroglobulin testing on Thyrogen was found to be more sensitive than thyroglobulin testing on TSHT. Specifically in a Phase III study involving 164 patients the detection rate of tissue of thyroid origin after a Thyrogen thyroglobulin test ranged from 73-87%, whereas, by using thyroglobulin on TSHT it was 42-62% for the same cut-off values and comparable reference standards.

Metastatic disease was confirmed by a post-treatment scan or by lymph node biopsy in 35 patients. Thyrogen-stimulated thyroglobulin levels were above 2 ng/mL in all 35 patients, whereas, thyroglobulin on THST was above 2 ng/mL in 79% of these patients.

Pre-therapeutic stimulation
In a comparator study involving 60 evaluable patients, the rates of successful ablation of thyroid remnants with 100 mCi/3.7 GBq (± 10%) radioiodine in post-thyroidectomy patients with thyroid cancer, were comparable for patients treated after thyroid hormone withdrawal versus patients treated after Thyrogen administration. Patients studied were adults (>18 years), with newly diagnosed differentiated papillary or follicular thyroid carcinoma, including papillary-follicular variant, characterised, principally (54 of 60), as T1-T2, N0-N1, M0 (TNM classification). Success of remnant ablation was assessed with radioiodine imaging and with serum thyroglobulin testing at 8 ± 1 months after treatment. All 28 patients (100%) treated after withdrawal of THST and all 32 patients (100%) treated after Thyrogen administration had either no visible uptake of radioiodine in the thyroid bed or, if visible, thyroid bed uptake <0.1% of the administered activity of radioiodine. The success of thyroid remnant ablation also was assessed by the criterion of Thyrogen-stimulated serum Tg level < 2 ng/mL eight months after ablation, but only in patients who were negative for interfering anti-Tg antibodies. Using this Tg criterion, 18/21 patients (86%) and 23/24 patients (96%) had thyroid remnants successfully ablated in the THST withdrawal group and the Thyrogen treatment group, respectively.

Quality of life was significantly reduced following thyroid hormone withdrawal, but maintained following either dosage regimen of Thyrogen in both indications.

A follow-up study was conducted on patients who previously completed the initial study, and data is available for 51 patients. The main objective of the follow-up study was to confirm the status of thyroid remnant ablation by using Thyrogen-stimulated radioiodine static neck imaging after a median follow-up of 3.7 years (range 3.4 to 4.4 years) following radioiodine ablation. Thyrogen-stimulated thyroglobulin testing was also performed.

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 considered ablated in the initial study were confirmed to be ablated in the follow-up study. In addition, no patient had a definitive 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 tumour from the regional disease noted at the start of the original study), and 2 patients could not be assessed.

In summary, in the pivotal study and its follow-up study, Thyrogen was non-inferior to thyroid hormone withdrawal for elevation of TSH levels for pre-therapeutic stimulation in combination with radioiodine for post-surgical ablation of remnant thyroid tissue.

Two large prospective randomised studies, the HiLo study (Mallick) and the ESTIMABL1 study (Schlumberger), compared methods of thyroid remnant ablation in patients with differentiated thyroid cancer who had been thyroidectomised. In both studies, patients were randomised 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, and patients were assessed about 8 months later. The HiLo study randomised 438 patients (tumour stages T1-T3, Nx, N0 and N1, M0) at 29 centres. As assessed by radioiodine imaging and stimulated Tg levels (n = 421), ablation success rates were approximately 86% in all four treatment groups. All 95% confidence intervals for the differences were within ±10 percentage points, indicating in particular non-inferiority of the low to the high radioiodine activity. Analyses of T3 patients and N1 patients showed that these subgroups had equally good ablation success rates as did lower-risk patients. The ESTIMABL1 study randomised 752 patients with low-risk thyroid cancer (tumour stages pT1 < 1 cm and N1 or Nx, pT1 >1-2 cm and any N stage, or pT2 N0, all patients M0) at 24 centres. Based on 684 evaluable patients, the overall ablation success rate assessed by neck ultrasounds and stimulated Tg levels was 92%, without any statistically significant difference among the four groups.

For the ESTIMABL1 study, 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).
The tables below provide long term follow up information for the ESTIMABL1 and HiLo studies

Table 1. ESTIMABL1 study recurrence rates in patients who received low or high dose RAI and those who prepared with Thyrogen or THW

	Thyrogen (N=374)	THW (N=378)
Total number of patients with recurrence (5.4 years)	7 (1,9%)	4 (1,1%)
Low activity RAI (1.1 GBq)	5 (1,3%)	1 (0,3%)
High activity RAI (3.7 GBq)	2 (0,5%)	3 (0,8%)

For the HiLo study, 434 (99%) of the original 438 patients were followed up for disease recurrence. The median follow-up was 6.5 years (4.5 to 7.6 years).

Table 2. HiLo study recurrence rates in patients who received low or high dose activity RAI

	Low activity dose RAI (1.1 GBq)	High activity dose RAI (3.7 GBq)
Total number of patients with recurrence	11	10
Recurrence rate (3 years)	1.5 %	2.1%
Recurrence rate (5 years)	2.1 %	2.7%
Recurrence rate (7 years)	5.9 %	7.3%

HR: 1.10 [95% CI 0.47 – 2.59]; p=0.83

Table 3. HiLo study recurrence rates in patients who prepared for ablation with Thyrogen or Thyroid Hormone Withdrawal

	Thyrogen	Thyroid Hormone Withdrawal (THW)
Total number of patients with recurrence	13	8
Recurrence rate (3 years)	1.5 %	2.1%
Recurrence rate (5 years)	2.1 %	2.7%
Recurrence rate (7 years)	8.3 %	5.0%

HR: 1.62 [95% CI 0.67 – 3.91], p=0.28

The long term follow-up data in ESTIMABL1 and HiLo confirmed similar outcomes for patients in all four treatment groups.

In summary, these studies support the efficacy of low activity radioiodine plus thyrotropin alpha (with reduced radiation exposure), Thyrothropin alfa was non-inferior to thyroid hormone withdrawal for pre-therapeutic stimulation in combination with radioiodine for post-surgical ablation of thyroid remnant tissue.

5.2 Pharmacokinetic properties
The pharmacokinetics of Thyrogen were studied in patients with well-differentiated thyroid cancer following a single 0.9 mg intramuscular injection. After injection, the mean peak (Cmax) level obtained was 116 ± 38 mU/L and occurred approximately 13 ± 8 hours after administration. The elimination half-life was 22 ± 9 hours. The major elimination route of thyrotropin alfa is believed to be renal and to a lesser extent hepatic.

5.3 Preclinical safety data
Non-clinical data are limited, but reveal no special hazard for humans from use of Thyrogen.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Mannitol
Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate
Sodium chloride

6.2 Incompatibilities
In the absence of compatibility studies, Thyrogen should not be administered as a mixture with other medicinal products in the same injection.

6.3 Shelf-life
Unopened vials
3 years.

Shelf-life after reconstitution
It is recommended that the Thyrogen solution be injected within three hours.
The reconstituted solution can be stored for up to 24 hours in a refrigerator (2°C - 8°C) under protection from light, while avoiding microbial contamination.

6.4 Special precautions for storage
Store in a refrigerator (2°C - 8°C).

Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and content of container
Clear Type I glass 5 mL vials. The closure consists of a siliconised butyl stopper with a tamper proof flip-off cap. Each vial contains 1.1 mg thyrotropin alfa. After reconstitution with 1.2 mL water for injection, 1.0 mL of solution (equal to 0.9 mg Thyrogen) is withdrawn and administered to the patient.

To provide sufficient volume to allow accurate dispensing, each vial of Thyrogen is formulated to contain an overfill of 0.2 mL.

Package size: Two vials of Thyrogen per carton.

6.6 Special precautions for disposal and other handling
The powder for solution for injection has to be reconstituted with water for injection. Only one vial of Thyrogen is required per injection. Each vial of Thyrogen is for single use only.

Use aseptic technique

Add 1.2 mL water for injection to the Thyrogen powder in the vial. Swirl the contents of the vial gently until all material is dissolved. Do not shake the solution. When the powder is dissolved the total volume in the vial is 1.2 mL. The pH of the Thyrogen solution is approximately 7.0.

Visually inspect the Thyrogen solution in the vial for foreign particles and discoloration. The Thyrogen solution should be a clear, colourless solution. Do not use vials exhibiting foreign particles, cloudiness or discoloration.
Withdraw 1.0 mL of the Thyrogen solution from the product vial. This equals 0.9 mg thyrotropin alfa to be injected.

Thyrogen does not contain preservatives. Throw away any unused solution immediately.
There are no special requirements for disposal.

The Thyrogen solution should be injected within three hours, however the Thyrogen solution will stay chemically stable for up to 24 hours, if kept in a refrigerator (between 2°C and 8°C). It is important to note that the microbiological safety depends on the aseptic conditions during the preparation of the solution.

HARUS DENGAN RESEP DOKTER

Manufactured by:
Genzyme Ireland Limited,
Waterford - Ireland

Packed & Released By:
Genzyme Corporation,
Northborough - MA 01532 USA

Registered By:
PT Kalventis Sinergi Farma,
Jakarta - Indonesia

PRESENTATION
Thyrogen
Box, 2 vials @ 1.1 mg thyrotropin alfa
Reg.No.: DKI1645300144A1

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

Date of text revision:
XXXX

SAP / ID. number : PIL Thyrogen-4 / XXXXXX
Film code : KSF/XXXXXX

Country : INDONESIA
Version number : 1
Date : 10.08.2023
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Pharmacode : XXXXX
Prepared by : Rahmat Hafid

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Printing Colour
Pantone Black

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For Pharmacode

Leaflet Kemasan: Informasi untuk Pengguna

Thyrogen®
Thyrotropin alfa untuk injeksi
Serbuk Liofil untuk cairan injeksi

genzyme
A SANOFI COMPANY
sanofi

Bacalah seluruh bagian leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena mengandung informasi penting bagi Anda.
- Simpanlah leaflet ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Jika Anda mengalami efek samping, bicarakan pada dokter atau apoteker anda. Hal ini termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini.

Apa yang ada dalam leaflet ini:

1. Apa Thyrogen itu dan apa kegunaannya

Thyrogen adalah human *Thyroid Stimulating Hormone* (TSH) yang diproduksi menggunakan proses bioteknologi.

Thyrogen digunakan untuk mendeteksi kanker thyroid jenis tertentu pada pasien yang kelenjar thyroidnya telah diangkat dan yang sedang menjalani pengobatan dengan hormon thyroid. Salah satu efeknya adalah bahwa produk tersebut merangsang sisa jaringan thyroid yang ada untuk mengambil Iodine yang diperlukan bagi radioiodine imaging. Di samping itu ia juga merangsang produksi hormon thyroid dan tiroglobulin jika ada jaringan thyroid yang tersisa. Hormon-hormon ini dapat diukur dalam darah Anda.

Thyrogen juga digunakan dengan pengobatan radioiodine untuk menghilangkan sisa jaringan thyroid yang mungkin ada setelah operasi pengangkatan kelenjar thyroid pada pasien yang tidak memiliki secondaries (metastasis) dan yang sedang menjalani pengobatan dengan hormon thyroid.

2. Apa yang Anda perlu ketahui sebelum menggunakan Thyrogen

Jangan gunakan Thyrogen
Katakan kepada dokter:
• jika Anda pernah mengalami **reaksi alergi** (misalnya, ruam atau gatal-gatal) terhadap *Thyroid Stimulating Hormone* (TSH) manusia ataupun sapi.
• jika Anda **alergi** terhadap salah satu dari bahan-bahan lainnya sebelum anda mengkonsumsi obat ini (semuanya tercantum dalam Bagian 6, juga pada akhir Bagian 2).
• jika Anda sedang **mengandung.**

Peringatan dan Perhatian
Bicaralah dengan dokter atau apoteker sebelum menggunakan Thyrogen jika Anda mengalami:
• penyakit ginjal yang memerlukan dialisis dan ia akan memutuskan berapa banyak Thyrogen yang tepat untuk Anda karena Anda mungkin rentan terhadap gangguan sakit kepala dan mual.
• penurunan fungsi ginjal dan ia akan memutuskan berapa banyak radioiodine yang dapat diberikan kepada Anda.
• penurunan fungsi hati, Anda tetap dapat menggunakan Thyrogen.

Efek pada pertumbuhan tumor
Pada pasien yang menderita kanker thyroid, dilaporkan bahwa terjadi pertumbuhan tumor selama penarikan hormon thyroid untuk prosedur diagnostik. Hal ini diduga terkait dengan peningtatan *Thyroid Stimulating Hormone* (TSH) untuk waktu yang lebih lama. Mungkin Thyrogen juga menyebabkan pertumbuhan tumor. Dalam sejumlah uji klinis hal itu tidak terlihat.

Karena TSH meningkat setelah penggunaan Thyrogen, pasien yang di dalam tubuhnya terdapat kanker sekunder yang bertumbuh (Metastasis) dapat mengalami pembengkakan lokal atau perdarahan di bagian Metastasis yang dapat menjadi lebih besar. Jika Metastasis tumbuh di celah-celah sempit misalnya intraserebral (di otak) atau di sumsum tulang belakang, pasien dapat mengalami gejala-gejala yang dapat terjadi dengan cepat misalnya kelumpuhan parsial pada satu sisi tubuh (hemiparesis), gangguan pernafasan atau kehilangan penglihatan.

Dokter Anda akan memutuskan apakah Anda termasuk kelompok pasien tertentu yang mungkin memerlukan pra-pengobatan dengan menggunakan kortikosteroid (misalnya, jika Anda mengalami pertumbuhan kanker sekunder di otak atau sumsum tulang belakang). Bicarakan dengan dokter Anda jika Anda mencemaskan hal tersebut.

Anak-anak
Karena kurangnya data penggunaan Thyrogen pada anak-anak, Thyrogen diberikan pada anak-anak hanya dalam keadaan tertentu.

Pasien berusia lanjut
Tidak diperlukan perhatian khusus untuk pasien berusia lanjut. Namun, jika kelenjar thyroid Anda belum diangkat sepenuhnya dan Anda juga menderita penyakit jantung, dokter Anda akan membantu Anda memutuskan apakah Thyrogen perlu diberikan kepada Anda.

Thyrogen dan obat-obatan lainnya
Tidak ada catatan tentang adanya interaksi obat dengan Thyrogen dan pengobatan hormon thyroid yang Anda mungkin sedang jalani.

Beritahu dokter atau apoteker Anda jika Anda sedang menjalani, baru saja selesai menjalani atau berencana menjalani pengobatan lainnya.

Dokter Anda akan menentukan aktivitas radioiodine yang tepat untuk radioiodine imaging, dengan mempertimbangkan fakta bahwa Anda melanjutkan pengobatan dengan hormon thyroid.

Kehamilan dan Menyusui
Mintalah saran dokter sebelum menggunakan obat apapun.

Jangan menggunakan Thyrogen jika Anda sedang mengandung. Jika Anda sedang mengandung atau menyusui, atau menduga Anda sedang mengandung atau berencana untuk memiliki anak, konsultasikan dengan dokter atau apoteker anda.

Thyrogen sebaiknya tidak diberikan kepada ibu menyusui. Menyusui sebaiknya dilanjutkan setelah mendapatkan saran dokter Anda.

Mengemudi dan Menggunakan Mesin
Beberapa pasien mungkin akan merasa pusing atau sakit kepala setelah pemberian Thyrogen yang dapat berdampak pada kemampuan mengemudi dan menggunakan mesin.

Informasi penting tentang sebagian dari bahan-bahan Thyrogen
Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per injeksi, dengan kata lain 'bebas natrium'.

3. Cara menggunakan Thyrogen

Dokter, perawat atau apoteker Anda akan mempersiapkan injeksi untuk Anda.
Pengobatan Anda harus diawasi oleh seorang dokter yang ahli dalam kanker tiroid. Serbuk Thyrogen harus dilarutkan dalam air injeksi. Cukup satu vial Thyrogen untuk setiap injeksi. Injeksi harus diberikan secara intra-muskular. Thyrogen tidak boleh dicampur dengan obat-obatan lain di dalam suntikan yang sama.

Dosis:
Dosis thyrogen yang direkomendasikan adalah dua dosis yang diberikan terpisah selama 24 jam. Dokter atau perawat anda akan menyuntikkan 1,0 ml larutan Thyrogen.

Thyrogen hanya untuk disuntikkan pada bagian otot pantat. Larutan Thyrogen tidak boleh disuntikkan ke dalam pembuluh darah vena.

Jika Anda mengalami:
• penurunan fungsi hati, Anda tetap dapat menjalani pengobatan dengan Thyrogen.
• penyakit ginjal yang mengharuskan dialisis dan dokter anda akan memutuskan berapa banyak Thyrogen yang dapat diberikan kepada Anda. Sebagian orang memiliki kerentanan lebih terhadap sakit kepala dan mual setelah menerima Thyrogen.
• penurunan fungsi ginjal, dokter anda akan memutuskan berapa banyak radioiodine yang dapat diberikan kepada Anda.

Ketika Anda menjalani penghapusan (*ablation*) atau *radioiodine imaging*, dokter akan memberi Anda radioiodine 24 jam setelah injeksi Thyrogen yang terakhir.
Scanning Diagnostik harus dilakukan 48 hingga 72 jam setelah pemberian radioiodine (72 hingga 96 jam setelah injeksi Thyrogen yang terakhir).
Scanning pasca pengobatan mungkin perlu ditunda beberapa hari hingga radioaktivitas yang melatarbelakanginya menurun.

Untuk pengujian thyroglobulin (Tg), dokter atau perawat anda akan mengambil sampel serum 72 jam setelah injeksi Thyrogen yang terakhir.

Penggunaan pada anak-anak
Dokter anak Anda dapat membantu Anda dalam memutuskan apakah Thyrogen perlu diberikan kepada anak Anda.

Overdosis
Jika Thyrogen yang diberikan kepada Anda melebihi yang diperlukan
Pasien yang tanpa disadari telah menerima Thyrogen melebihi yang diperlukan mengalami mual, lemah tubuh, pusing, sakit kepala, muntah dan badan terasa panas kemerah-merahan.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter anda.

4. Kemungkinan efek samping

Sebagaimana obat-obatan lainnya, obat ini dapat menimbulkan efek samping, meskipun tidak semua orang mengalami -nya.
Dampak-dampak yang dikaitkan dengan penggunaan Thyrogen adalah sebagai berikut:

Sangat umum (lebih dari 1 pengguna dalam 10 orang mengalami dampak):
• mual

Umum (1 hingga 10 pengguna dari 100 orang mengalami dampak):
• muntah
• kelelahan
• pusing
• sakit kepala
• diare,
• lemah tubuh,
• serasa ditusuk-tusuk jarum atau kesemutan (parestesia).

Jarang (1 hingga 10 pengguna dari 1.000 orang mengalami dampak):
• merasa panas
• hives (urticaria)
• ruam
• gejala flu
• demam
• menggigil
• nyeri punggung

Frekuensi tidak diketahui
(Frekuensi tidak dapat diperkirakan dari data yang tersedia)
• pembengkakan tumor
• nyeri (termasuk nyeri di bagian metastasis (pertumbuhan kanker sekunder))
• tremor
• stroke
• palpitasi
• kulit memerah
• sesak napas
• gatal (pruritus)
• keringat berlebihan
• nyeri otot atau sendi
• reaksi di titik injeksi (meliputi: kemerahan, rasa tidak nyaman, gatal, merasa nyeri seperti sengatan atau nyeri lokal, dan ruam gatal)
• hipersensitivitas (reaksi alergi), reaksi ini meliputi hives (urticaria), gatal-gatal, kulit memerah, kesulitan bernapas dan ruam.

Kasus yang sangat jarang dari **hiperthyroidisme** (peningkatan aktivitas kelenjar tiroid) atau **fibrilasi atrium** telah dilaporkan ketika Thyrogen diberikan kepada pasien-pasien yang tidak mengalami pengangkatan kelenjar Thyroid secara total ataupun sebagian.

Stroke sangat jarang terjadi pada pasien wanita. Belum dapat dipastikan apakah stroke terkait dengan pemberian Thyrogen.

Jika Anda mengalami efek samping, bicarakan dengan dokter atau apoteker. Hal ini termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini.

5. Bagaimana Menyimpan Thyrogen
Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kadaluwarsa yang tertera pada label setelah huruf "EXP". Tanggal kadaluwarsa mengacu pada hari terakhir dari bulan itu.

Simpan dalam lemari es (2°C - 8°C).

Simpan vial di dalam karton luar agar tidak langsung terkena cahaya.

Jangan gunakan obat ini jika Anda menyadari adanya partikel asing, keruh, atau berubah warna.

Jangan membuang obat apapun melalui air limbah atau limbah rumah tangga. Tanyakan kepada apoteker bagaimana cara membuang obat-obatan yang Anda tidak gunakan lagi. Langkah-langkah ini akan membantu melestarikan lingkungan.

6. Batas Kadaluwarsa

Vial yang belum dibuka
3 tahun

Batas kadaluwarsa setelah rekonstitusi
Disarankan agar Larutan Thyrogen disuntikkan dalam waktu 3 jam.
Larutan yang telah direkonstitusi dapat disimpan hingga 24 jam di lemari es (2°C - 8°C) di bawah lindungan dari cahaya, sambil menghindari kontaminasi mikroba.

7. Ketidaktercampuran

Thyrogen tidak boleh diberikan bersama obat-obatan yang lain dalam satu suntikan.

8. Isi kemasan dan informasi lainnya

Apa saja yang terkandung dalam Thyrogen

Zat aktifnya adalah thyrotropin alfa.
Setiap vial mengandung 0,9 mg/ml thyrotropin alfa pada saat direkonstitusi dengan air sebanyak 1,2 mL untuk injeksi. Cukup 1 ml yang diperlukan atau setara dengan 0,9 mg thyrotropin alfa.

Bahan-bahan lainnya adalah:
• mannitol
• monosodium fosfat, monohidrat
• disodium fosfat, heptahidrat
• Natrium klorida

(Lihat **pada akhir** Bagian 2 "Informasi penting tentang beberapa bahan Thyrogen")

Apa ciri-ciri fisik Thyrogen dan isi kemasan

Bubuk untuk larutan injeksi. Bubuk liofil tersebut berwarna putih bersih hingga putih keruh.

Ukuran kemasan: Dua vial Thyrogen per dus.

HARUS DENGAN RESEP DOKTER

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Waterford - Ireland

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PRESENTASI
Thyrogen
Kotak, 2 vial @1.1 mg thyrotropin alfa
Reg.No.: DKI1645300144A1

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

DISETUJUI BPOM 25 AGUSTUS 2023

ID REG : EREG100022VR12300425