ANNEX 1

SUMMARY OF PRODUCT CHARACTERISTICS

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 lyophilised 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 rhTSH-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
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 elderly (see section 4.4).

Patients with 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 thyroid stimulating hormone (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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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.

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 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.

Sodium
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 Sanofi 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).

MedDRA System Organ Class	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 reactions
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. It is not recommended to perform TSH assays after Thyrogen administration. The occurrence of antibodies which could interfere with endogenous TSH assays performed during regular follow-ups 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 pre-treatment with corticosteroids be considered for patients in whom local tumour expansion may compromise vital anatomic structures.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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.

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 reestablishment of fluid balance and administration of an antiemetic 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 (T_3) and thyroxine (T_4).

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 radioiodineactivity. 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). Thyrotropin 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 (C_{max}) 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, this medicinal product must 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 after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents 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: one or two vials per carton.

Not all pack sizes may be marketed.

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. Dispose of any unused solution immediately. 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.

7. MARKETING AUTHORISATION HOLDER

Sanofi B.V., Paasheuvelweg 25, 1105 BP Amsterdam, The Netherlands

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/122/001
EU/1/99/122/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 March 2000
Date of last renewal: 9 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Genzyme Corporation.
45, 51, 68, 74, 76 and 80 New York Avenue
Framingham, MA 01701-
United States

Name and address of the manufacturers responsible for batch release

Genzyme Ireland Limited
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - PACK OF 1 VIAL
OUTER CARTON - PACK OF 2 VIALS

1. NAME OF THE MEDICINAL PRODUCT

THYROGEN 0.9 mg powder for solution for injection.
Thyrotropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 0.9 mg/ml of thyrotropin alfa when reconstituted with 1.2 ml water for injection.

3. LIST OF EXCIPIENTS

Excipients:
Mannitol
Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate
Sodium chloride
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection.
2 vials of powder for solution for injection equal to 2 doses to be administered at a 24-hour interval.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular injection only.
Only 1 ml should be withdrawn equal to 0.9 mg of thyrotropin alfa.
Administration within 3 hours after reconstitution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C).
Keep the vial in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only.
Any unused solution should be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/122/001
EU/1/99/122/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

<PC:
SN:
NN:>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

THYROGEN 0.9 mg powder for solution for injection.
thyrotropin alfa
Intramuscular use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Store in a refrigerator (2°C - 8°C).

Sanofi B.V.- NL

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Thyrogen 0.9 mg powder for solution for injection
Thyrotropin alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist**.**
- If you experience any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Thyrogen is and what it is used for

Thyrogen contains the active substance thyrotropin alfa. Thyrogen is a human thyroid stimulating hormone (TSH) manufactured using biotechnology processes.

Thyrogen is used to detect certain types of thyroid cancer in patients who have had their thyroid gland removed and who are taking thyroid hormones. One of the effects is that it stimulates any remaining thyroid tissue to take up iodine which is important for radioiodine imaging. It also stimulates the production of thyroglobulin and thyroid hormones if there is any thyroid tissue left. These hormones can be measured in your blood.

Thyrogen is also used with radioiodine treatment to eliminate (ablate) the thyroid tissue left over after surgical removal of the thyroid gland (remnant) in patients who do not have secondary cancer growths (metastases) and who are taking thyroid hormone.

2. What you need to know before you use Thyrogen

Do not use Thyrogen:
- if you are allergic to bovine or human thyroid stimulating hormone (TSH) or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant.

Warnings and precautions
Talk to your doctor or pharmacist before using Thyrogen
- if you have kidney disease that requires dialysis and he will decide how much Thyrogen to give to you as you may have more chance of experiencing headache and nausea.
- if you have reduced kidney function and he will decide how much radioiodine to give you.

- if you have reduced liver function; you should still be able to receive Thyrogen.

Effect on tumour growth
In patients with thyroid cancer, tumour growth has been reported during withdrawal of thyroid hormones for diagnostic procedures. This was thought to be related to the elevated thyroid stimulating hormone (TSH) levels over a longer period. It is possible that Thyrogen may also cause tumour growth. In clinical trials this was not seen.

Due to elevation of TSH levels after Thyrogen, patients with secondary cancer growths (metastases) can experience local swelling or bleeding at the site of these metastases which may become bigger. If the metastases are present in narrow spaces e.g. intracerebral (in the brain) or in the spinal cord, patients could experience symptoms which can occur quickly such as partial paralysis affecting one side of the body (hemiparesis), breathing problems or loss of vision.

Your doctor will decide if you belong to a specific group of patients for which pre-treatment with corticosteroids is to be considered (for example, if you have secondary cancer growths in your brain or spinal cord). Please talk to your doctor about this if you have concerns.

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

Elderly
No special precautions for elderly patients are necessary. However, if your thyroid gland has not been removed completely and you are also suffering from heart disease, your doctor will help you decide if Thyrogen should be given to you.

Other medicines and Thyrogen
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

There are no known drug interactions with Thyrogen and the thyroid hormones you may be taking.

Your doctor will determine the exact activity of radioiodine to use for radioiodine imaging, taking into consideration the fact that you continue to take thyroid hormones.

Pregnancy and breast-feeding
Do not take Thyrogen if you are pregnant. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Thyrogen should not be given to breast-feeding women. Breast-feeding should only be resumed following advice from your doctor.

Driving and using machines
Some patients may feel dizzy or have headaches after administration of Thyrogen which may affect the ability to drive and use machines.

Thyrogen contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

3. How to use Thyrogen

Your medicine will be injected by a doctor or a nurse.

Your treatment should be supervised by a doctor who has expertise in thyroid cancer. Thyrogen powder must be dissolved in water for injection. Only one vial of Thyrogen is required per injection. Thyrogen should only be administered into the buttock muscle. This solution should never be injected into a vein. Thyrogen must not be mixed with other medicines in the same injection.

The recommended dose of Thyrogen is two doses administered 24 hours apart. Your doctor or nurse will inject 1.0 ml of the Thyrogen solution.

When you undergo radioiodine imaging or elimination (ablation), your doctor will give you radioiodine 24 hours after your final Thyrogen injection.
Diagnostic scanning should be performed 48 to 72 hours after the radioiodine administration (72 to 96 hours after the final injection of Thyrogen).
Post-treatment scanning may be delayed a few days to allow background radioactivity to decline.

For thyroglobulin (Tg) testing, your doctor or nurse will take a serum sample 72 hours after the last injection of Thyrogen.

Use in children
Your child's doctor will help you decide if Thyrogen should be given to your child.

If you are given more Thyrogen than you should receive
Patients who accidentally received too much Thyrogen have reported nausea, weakness, dizziness, headache, vomiting and hot flashes.

A suggested treatment in case of overdose would be the reestablishment of fluid balance and administration of an antiemetic may also be considered.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following effects have been reported with Thyrogen:

Very common (may affect more than 1 in 10 people):
- nausea

Common (may affect up to 1 in 10 people):
- vomiting
- fatigue
- dizziness
- headache
- weakness

Uncommon (may affect up to 1 in 100 people):

- feeling hot
- hives (urticaria)
- rash
- flu symptoms
- fever
- chills
- back pain
- diarrhoea
- prickling or tingling sensation (paraesthesia),
- neck pain
- inability to taste (ageusia)
- impaired sense of taste (dysgeusia)
- influenza

Not known (frequency cannot be estimated from the available data):

- swelling of the tumour
- pain (including pain at the site of metastases (secondary cancer growths))
- tremor
- stroke
- palpitations
- flushing
- shortness of breath
- itching (pruritus)
- excessive sweating
- muscle or joint pain
- injection site reactions (including redness, discomfort, itching, local pain or stinging, and an itchy rash)
- low TSH
- hypersensitivity (allergic reactions), these reactions include hives (urticaria), itching, flushing, difficulty in breathing and rash.

Very rare cases of **hyperthyroidism** (increased activity of the thyroid gland) or **atrial fibrillation** have been reported when Thyrogen was administered to patients who had not undergone total or partial removal of the thyroid gland.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Thyrogen

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

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

It is recommended that the Thyrogen solution be injected within three hours after reconstitution.
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.

Do not use this medicine if you notice foreign particles, cloudiness or discoloration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Thyrogen contains

- The active substance is thyrotropin alfa.

Each vial contains 0.9 mg/ml of thyrotropin alfa when reconstituted with 1.2 ml water for injection. Only 1 ml should be withdrawn equal to 0.9 mg of thyrotropin alfa.

- The other ingredients are:

Mannitol
Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate
Sodium chloride.

Thyrogen contains sodium, see section 2.

What Thyrogen looks like and contents of the pack

Powder for solution for injection. White to off-white lyophilised powder.

Pack sizes: one or two vials of Thyrogen per carton.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
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The Netherlands

Manufacturer:
Genzyme Ireland Limited
IDA Industrial Park
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Waterford
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

The recommended dose regimen of Thyrogen is two intramuscular injections of 0.9 mg thyrotropin alfa administered at a 24-hour interval.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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. Dispose of any unused solution immediately. No special requirements for disposal.

After reconstitution, the solution should 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. It is important to note that the microbiological safety depends on the aseptic conditions during the preparation of the solution.