Professional Information for THYROGEN®

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

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/mL thyrotropin alfa.

Contains sugar: 29 mg/mL mannitol (following reconstitution).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

A sterile, non-pyrogenic, white to off-white lyophilised cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

THYROGEN is indicated for use as:

- An adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with/without whole body radioiodine imaging undertaken for the detection of thyroid remnants and differentiated thyroid cancer in post-thyroidectomy patients maintained on thyroid hormone suppression therapy (THST).

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

4.2 Posology and method of administration

Posology

A two-injection regimen is recommended for THYROGEN administration.

The two-injection regimen is THYROGEN 0,9 mg administered intramuscularly (IM), followed by a second 0,9 mg IM injection 24 hours later.

After reconstitution with 1,2 mL sterile water for injection, 1,0 mL solution (0,9 mg thyrotropin alfa) is administered by intramuscular injection to the buttock.

For radioiodine imaging or treatment, radioiodine should be administered 24 hours following the final THYROGEN injection. Diagnostic scanning should be performed 48 hours after radioiodine administration, whereas post-therapy scanning may be delayed additional days to allow background activity to decline.

The following parameters, as utilised in clinical trials, are recommended for radioiodine diagnostic scanning with THYROGEN:

- Use a diagnostic activity of 4 mCi (148 MBq) radioiodine (^{131}I).
- Whole body images should be acquired for a minimum of 30 minutes and/or containing a minimum of 140 000 counts.
- Scanning times for single (spot) images of body regions should be 10 – 15 minutes or less if the minimum number of counts is reached sooner (i.e. 60 000 for a large field of view camera, 35 000 counts for a small field of view).

Please see section 4.4, “Considerations prior to THYROGEN administration”, for the selection of an appropriate activity of ^{131}I for remnant ablation. For radioiodine ablation of thyroid tissue remnants, the activity of ^{131}I is carefully selected at the discretion of the nuclear medicine specialist.

For serum thyroglobulin (Tg) testing, the serum sample should be obtained 72 hours after the final injection of THYROGEN.

Special populations

Children younger than 18 years:

Neither safety nor effectiveness in patients below the age of 18 years has been established in clinical trials.

Elderly patients:

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.

Careful evaluation of benefit-risk relationships should be assessed for high risk elderly patients with functioning thyroid tumours and/or patients with heart disease (e.g. valvular heart disease, cardiomyopathy, coronary artery disease, and prior or current tachydysrhythmia) undergoing THYROGEN administration.

Renal insufficiency:

In patients with significant renal impairment, the activity of ^{131}I should be carefully selected by the nuclear specialist.

Hepatic insufficiency:

Studies in patients with hepatic insufficiency have not been performed.

Method of administration

After reconstitution with sterile 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 THYROGEN before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to thyrotropin alfa or any of the components of THYROGEN (see section 6.1).

4.4 Special warnings and precautions for use

Considerations prior to THYROGEN administration:

Health care practitioners knowledgeable in the management of patients with thyroid cancer should administer THYROGEN.

THYROGEN should be administered intramuscularly only. It should not be administered intravenously. Caution should be exercised when THYROGEN is administered to patients who have been previously treated with bovine TSH and, in particular, to those patients who have experienced hypersensitivity reactions to bovine TSH.

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.

Due to elevation of TSH levels after THYROGEN administration, thyroid cancer patients with metastatic disease, particularly in confined spaces (for example the brain, spinal cord, orbit or soft tissues of the neck) may be subject to local oedema or focal haemorrhage at the site of these metastases. It is recommended that pretreatment with corticosteroids be considered in these patients in whom local tumour expansion may compromise vital anatomic structures prior to the administration of THYROGEN.

Considerations post-THYROGEN administration:

In the clinical trials performed, the combination of whole body scanning (WBS) and thyroglobulin (Tg) testing after THYROGEN administration increased the detection rate for remnant thyroid tissue or cancer when compared to either diagnostic test alone. False negative results may occur with THYROGEN. If a high index of suspicion for metastatic disease persists, a confirmatory withdrawal diagnostic or post-therapy WBS and Tg testing should be considered.

Renal impairment:

The organ(s) of recombinant human TSH (rhTSH) clearance in humans have not been identified, but studies of pituitary-derived TSH suggest the involvement of the liver and kidneys. 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. ESRD patients who receive THYROGEN may have markedly elevated TSH levels for up to two weeks after treatment, which 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.

Useful laboratory tests for monitoring patients:

No specific tests are indicated routinely for monitoring thyroid cancer patients after receiving THYROGEN.

Sodium:

THYROGEN contains less than 1 mmol sodium (23 mg) per vial and is essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

Other medicines:

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 (T3) and thyroxine (T4), when administered concurrently.

Food:

None known.

Laboratory tests:

In clinical trials, the reference standard for determining whether patients had thyroid remnant or cancer present was a hypothyroid Tg ≥ 2,0 ng/mL and/or a hypothyroid scan (either diagnostic or post-therapy). This analysis evaluated whether Tg testing after THYROGEN administration improved the diagnostic sensitivity of a Tg test in patients with a negative Tg on thyroid hormone suppression therapy (THST) using a cut-off of 2,0 ng/mL. It should be noted that THYROGEN-Tg levels are generally lower than hypothyroid-Tg levels and thus health care practitioners may need to use a lower Tg cut-off level when using THYROGEN than would be used with a hypothyroid-Tg.

The use of THYROGEN allows for radioiodine imaging while patients are euthyroid on T_3 and/or T_4. Data on radioiodine kinetics indicate that the clearance of radioiodine is approximately 50 % greater while euthyroid than during the hypothyroid state, thus resulting in less radioiodine retention in the body at the time of imaging. This difference in radioiodine clearance is caused by decreased renal function in the hypothyroid state. This factor should be considered when selecting the activity of radioiodine for use in radioiodine imaging.

4.6 Fertility, pregnancy and lactation

Safety of THYROGEN in pregnancy and lactation has not been established.

It is not known whether THYROGEN is excreted in human milk.

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 common adverse reactions reported in clinical trials were 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 post-marketing.

Side effects have been reported according to the following categories:

Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 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 (including cysts and polyps):			

			Neoplasm swelling, metastatic pain
Nervous system disorders:			
	Dizziness, headache, paraesthesia	Ageusia, dysgeusia	Stroke, tremor
Cardiac disorders:			
			Palpitations
Vascular disorders:			
			Flushing
Respiratory, thoracic and mediastinal disorders:			
			Dyspnoea
Gastrointestinal disorders:			
Nausea	Vomiting, diarrhoea		
Skin and subcutaneous tissue disorders:			
		Urticaria, rash	Pruritus, hyperhidrosis
Musculoskeletal and connective tissue disorders:			
		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

THYROGEN administration may cause transient (< 48 hours) influenza-like symptoms (also called flu-like symptoms (FLS)), which may include fever (> 38 °C), chills, shivering, myalgia, arthralgia, fatigue, asthenia, malaise and headache (non-focal).

Very rare cases of hyperthyroidism or atrial fibrillation have been observed when 0,9 mg of THYROGEN has been administered in patients with presence of either partial or entire thyroid gland.

In clinical trials, no patients have developed antibodies to thyrotropin alfa, either after single or repeated (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.

Very rare manifestations of hypersensitivity to THYROGEN have been reported in clinical, post-marketing settings and in special treatment programmes involving patients with advanced disease: these are urticaria, rash, pruritus, flushing, and respiratory signs and symptoms.

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 pain at the site of metastasis, and respiratory distress requiring tracheotomy 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.

Post-marketing:

Post-marketing adverse reaction data from patients who received THYROGEN as an adjunctive treatment for radioiodine ablation of thyroid tissue remnants who have undergone a thyroidectomy for well-differentiated thyroid cancer and from patients who received THYROGEN for diagnostic purposes did not differ from adverse reaction data from the clinical trials. These adverse reactions include headache, fatigue, vomiting, dizziness, paraesthesia, asthenia, diarrhoea and injection site reactions (e.g. discomfort, pain, and pruritus at the injection site).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of THYROGEN is important. It allows continued monitoring of the benefit/risk balance of THYROGEN. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel),

or

- SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

See section 4.8. Treatment is symptomatic and supportive.

Data on exposure above the recommended dose is limited to clinical studies and a special treatment programme. Three patients in clinical trials and one patient in the special treatment programme 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, the event 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 programme, a 77-year-old patient 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.3 Thyroid preparations.

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, anterior pituitary lobe hormones and analogues.

ATC code: H01AB01

Thyrotropin alfa is a recombinant human thyroid stimulating hormone (rhTSH). Binding of thyrotropin alfa to TSH receptors on normal thyroid epithelial cells or on well-differentiated thyroid cancer tissue stimulates iodine uptake and organification, and synthesis and secretion of thyroglobulin, T3 and T4.

In clinical studies with thyrotropin alfa, decreased clearance of ^{131}I during the hypothyroid state complicated comparisons between ^{131}I uptake observed in the thyroid bed when the patient was euthyroid after thyrotropin alfa administration versus uptake while the patient was in a hypothyroid state.

The use of THYROGEN allows for radioiodine imaging while patients are euthyroid on T3 and/or T4. 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. These factors should be considered when selecting the activity of radioiodine for use in radioiodine imaging.

5.2 Pharmacokinetic properties

The pharmacokinetics of thyrotropin alfa were studied in 16 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 organ(s) of TSH clearance in humans have not been identified, but studies of pituitary-derived TSH suggest the involvement of the liver and kidneys.

In two Phase 3 clinical studies, TSH levels were measured. In one study, mean serum TSH levels were 101 ± 60 mU/L and 132 ± 89 mU/L 24 hours after the first and second doses, respectively, and 16 ± 12 mU/L 72 hours after the second dose of thyrotropin alfa 0,9 mg IM. The baseline TSH was 0,2 ± 0,3 mU/L prior to thyrotropin alfa administration. In the second Phase 3 study, thyrotropin alfa was administered as 0,9 mg every 24 hours for two doses (2-dose regimen) or 0,9 mg every 72 hours for three doses (3-dose regimen). The maximal serum TSH level was 124 ± 59 mU/L 24 hours after the second dose in the 2-dose regimen (baseline 0,08 ± 0,17 mU/L); TSH levels remained above 25 mU/L for approximately four days. The maximal serum TSH level was 102 ± 44 mU/L 24 hours after the final dose in the 3-dose regimen (baseline 0,10 ± 0,13 mU/L); TSH levels were ≥ 25 mU/L for approximately nine days.

5.3 Preclinical safety data

Non-clinical data are limited, but reveal no special hazard for humans from the use of THYROGEN.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

Sodium chloride

Sodium phosphate dibasic heptahydrate

Sodium phosphate monobasic monohydrate.

6.2 Incompatibilities

None known. Injection material should not be mixed with other substances.

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 at a temperature of 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 to protect from light.

Do not freeze or shake the reconstituted solution.

For storage conditions after reconstitution of THYROGEN, see section 6.3.

6.5 Nature and contents of container

THYROGEN is packed into a 5 mL Type I flint glass vial with a grey rubber stopper and sealed with an aluminium seal with a dark blue polypropylene flip-off cap.

Each vial of THYROGEN contains 1,1 mg of thyrotropin alfa. After reconstitution with 1,2 mL sterile water for injection, 1,0 mL of solution (equal to 0,9 mg thyrotropin alfa) is withdrawn and administered to the patient.

Pack size: Two vials of THYROGEN are packed in an outer container with the professional information.

6.6 Special precautions for disposal and other handling

The powder for solution should be reconstituted immediately prior to use with sterile water for injection.

Only one vial of THYROGEN is required per injection.

Each vial of THYROGEN is intended for single use.

Reconstitution and dilution (using aseptic technique):

Add 1,2 mL sterile 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 reconstituted THYROGEN solution is approximately 7,0.

Visually inspect the THYROGEN solution in the vial for foreign particles and discolouration. The THYROGEN solution should be a clear, colourless solution. Do not use vials exhibiting foreign particles, cloudiness or discolouration.

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. 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

8. REGISTRATION NUMBER

43/21.3/0869

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 October 2012

10. DATE OF REVISION OF THE TEXT

14 February 2022