18 October 2012
EMA/CHMP/709596/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Thyrogen

thyrotropin alfa

Procedure No.: EMEA/H/C/000220/II/0059

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Genzyme Europe B.V. submitted to the European Medicines Agency on 5 July 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Thyrogen	thyrotropin alfa	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of section 4.1 of the SmPC in order to recommend the use of Thyrogen with a range of 30-100 mCi ^{131}I for postoperative thyroid remnant ablation, as opposed to the currently approved 100 mCi ^{131}I, based on the results of two published studies (HiLo and ESTIMABL). Sections 4.4, 4.5 and 5.1 were proposed to be updated accordingly to amend relevant existing warnings and to include information from the two studies. In addition, the MAH took the opportunity to make minor editorial amendments in the SmPC, to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 8.1.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Rapporteur: Patrick Salmon

1.2. Steps taken for the assessment

Submission date:	5 July 2012
Start of procedure:	22 July 2012
Rapporteur's assessment report circulated on:	27 August 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 September 2012
MAH's responses submitted to the CHMP on:	26 September 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	5 October 2012
CHMP opinion:	18 October 2012

2. Scientific discussion

2.1. Introduction

Thyrogen contains thyrotropin alfa, a recombinant form of the human Thyroid Stimulating Hormone (TSH) with comparable biochemical properties to natural TSH. Binding of thyrotropin alfa to TSH receptors on thyroid epithelial cells stimulates iodine uptake and organification, and synthesis and release of thyroglobulin (Tg), triiodothyronine (T_3) and thyroxine (T_4).

Thyrogen is indicated for use with serum Tg testing with or without radioiodine imaging for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on thyroid hormone suppression therapy (THST). Low risk patients with well-differentiated thyroid carcinoma who have undetectable serum Tg levels on THST and no rhTSH-stimulated increase of Tg levels may be followed-up by assaying rhTSH-stimulated Tg levels.

Thyrogen is also indicated for pre-therapeutic stimulation in combination with 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.

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

With this variation application, the Marketing Authorisation Holder (MAH) proposed to change the recommended dose of ^{131}I from 100mCi to the range of 30-100 mCi for the approved remnant ablation indication. This request is based on the results of two recently published papers:

- Mallick U, Harmer C, Yap B, *et al.* Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. N Engl J Med, 2012; 366: 1674-1685 (HiLo study)

- Schlumberger M, Catargi B, Borget I, *et al.* Strategies of radioiodine ablation in patients with low-risk thyroid cancer. N Engl J Med, 2012; 366: 1663-1673 (ESTIMABL study)

The variation application was also intended to fulfil FUM 035 which resulted from the approval of variation EMEA/H/C/000220/II/0038 (EC Decision date: 20 January 2010) that extended the indication for Thyrogen (thyrotropin alpha) to include use of Thyrogen in combination with 100 mCi of radioiodine for ablation of thyroid tissue. With FUM 035 the MAH had committed to provide the results of the investigator-sponsored study HiLo conducted in the UK, particularly with regard to tumour stage T3 patient results.

Consequently, changes to sections 4.1. 4.4, 4.5 and 5.1 of the SmPC were proposed. In addition, the MAH has also taken the opportunity to make minor editorial amendments, to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 8.1. Finally, an updated RMP was submitted to reflect PI changes and additional editorial changes were made to the RMP.

2.2. Clinical aspects

2.2.1. Introduction

Post-surgical thyroid remnant ablation is performed in between 60 and 80% of patients who have differentiated thyroid cancer in the U.S. and in Europe. This procedure removes the residual normal thyroid tissue, allows radioiodine imaging to be performed at the time of the ablation procedure (which could detect unsuspected thyroid tumour), makes subsequent radioiodine scans more informative, and

lowers the TSH stimulated serum Tg level to allow easier follow-up of patients for tumour recurrences. The procedure may also remove residual thyroid tumour cells still present in the patient after surgery.

For several decades after the first introduction of radioiodine therapy, this first treatment with ^{131}I was performed on thyroidectomised patients who were clinically hypothyroid and who had elevated their endogenous serum levels of thyroid stimulating hormone (TSH). This elevation of serum TSH is necessary for radioiodine to be optimally taken up by thyroid cells and covalently bound (organified) to protein so that the ^{131}I can remain localised and has an optimal killing effect within the thyroid cells. An alternative preparatory method using exogenous injection of recombinant human TSH (rhTSH; Thyrogen) was developed during the 1990s. Use of rhTSH allows patients to remain euthyroid (with all the associated advantages) and euthyroid state also reduces the radiation exposure to the patient's whole body, blood and bone marrow because when euthyroid, the renal clearance of ^{131}I is greater as compared with when the patients are hypothyroid.

Use of radioiodine for these thyroid cancer patients is generally safe, but the risks and benefits of radiation need to be weighed carefully. Because of immediate tissue damage (salivary glands, lacrimal glands, bone marrow, gonads, and because of the concern about potential induction of other malignancies years after the ablation procedure, many clinicians for years have preferred to adjust the amount of radioiodine used based on the seriousness of the patient's thyroid cancer status.

Regarding use of Thyrogen for remnant ablation, although there was appropriate evidence of efficacy for Thyrogen when used with 100 mCi ^{131}I (3.7 GBq), there were only limited data available when used with 30 mCi (1.1 GBq) and different studies gave different results.

In the United Kingdom, 2007 guidelines recommend the use of high-dose radioiodine. Guidelines of the U.S. National Comprehensive Cancer Network (2010), the American Thyroid Association (2009) and a European consensus report (2006) indicate that clinicians can choose between the low dose and the high dose. However, reliable evidence was lacking.

2.2.2. Clinical Efficacy aspects

The applicant has provided the results of two recently published large, prospective randomised trials with 2x2 factorial designs which specifically address the issue of dose of radiation used in remnant ablation, comparing the currently approved 100mCi (3.7GBq) with the lower 30mCi (1.1GBq). In addition, one of the two studies (Mallick, 2012, N Engl J Med) enrolled a patient population that provides insight into remnant ablation in patients originally diagnosed with primary tumours classed as T3 (TNM staging system, 6th edition).

HiLo Study

The HiLo study (Mallick *et al*, 2012) was a randomised non-inferiority trial comparing low-dose and high-dose radioiodine, each in combination with either thyrotropin alpha or thyroid hormone withdrawal before ablation, performed in the UK in 438 patients with differentiated thyroid cancer.

The patients, aged between 16 and 80 years, were tumour stage pT1-T3, with possible spread to nearby lymph nodes but without metastasis, Nx, N0 or N1, and M0 (TNM 6th edition). They had undergone total thyroidectomy with or without lymph node dissection.

Patients were randomised to one of four arms: 30 mCi or 100 mCi, each with either rhTSH or withdrawal of thyroid hormone as preparation.

Ablation success was determined 6 to 9 months later by using ^{131}I diagnostic scanning, and by measurement of stimulated serum Tg levels (using withdrawal of thyroid hormone in 140 cases, and Thyrogen in the rest). Ablation success was based on a diagnostic scan thyroid bed uptake of <0.1% of

the administered activity of ^{131}I, and stimulated serum Tg <2.0 ng/mL. The study was sized assuming an 80% success rate for the 100 mCi regimens, and treatments were to be judged comparable if the ablation success rates fell within a maximum allowable difference of 10 percentage points.

Recruitment occurred at 29 centres from 2007 to 2010. The median patient age was 44 years, and about 80% of the patients were female. In total, 23% of the patients were T3 and 16% were N1. Data could be analysed for 421 patients. Of these, 207 patients received high dose radioiodine (105 had thyroid hormone withdrawal and 102 received Thyrogen) and 214 patients received low dose radioiodine (106 had thyroid hormone withdrawal and 108 received Thyrogen).

Ablation success rates at 6 to 9 months for the four subgroups of the study are summarised in the following Table 1.

Table 1: Ablation Success Rates at 6 to 9 Months in the four subgroups of study HiLo

Variable	1.1 GBq + rhTSH	3.7 GBq + rhTSH	1.1 GBq + THW	3.7 GBq + THW
Ablation success based on diagnostic scan alone — no./total no. (%)	100/108 (92.6)	97/102 (95.1)	98/106 (92.5)	100/105 (95.2)
Ablation success based on thyroglobulin alone — no./total no. (%)	81/96 (84.4)	81/89 (91.0)	78/90 (86.7)	72/84 (85.7)
Ablation success based on both diagnostic scan and thyroglobulin — no./total no. (%)	91/108 (84.3)	92/102 (90.2)	91/106 (85.8)	92/105 (87.6)

Ablation success rates at 6 to 9 months according to four comparisons of radioiodine doses and methods of preparation are summarised in the following Table 2.

Table 2: Ablation Success Rates at 6 to 9 Months, According to Four Comparisons of Radioiodine Doses and Methods of Preparation

Variable	Comparison 1		Comparison 2		Comparison 3		Comparison 4	
	1.1 GBq (30mCi)	3.7 GBq (100mCi)	THW	rhTSH	1.1 GBq +rhTSH	3.7 GBq + THW	1.1 GBq +rhTSH	3.7 GBq +rhTSH
Ablation success based on diagnostic scan alone - no./total no. (%)	198/214 (92.5)	197/207 (95.2)	198/211 (93.8)	197/210 (93.8)	100/108 (92.6)	100/105 (95.2)	100/108 (92.6)	97/102 (95.1)
Risk difference (%) (95% CI)	-2.7 (-7.2 to 1.9)		-0.03 (-4.6 to 4.6)		-2.6 (-9.0 to 3.7)		-2.5 (-9.0 to 4.0)	
P value	0.26		0.99		0.42		0.45	
Ablation success based on thyroglobulin alone - no./total no. (%)	159/186 (85.5)	153/173 (88.4)	150/174 (86.2)	162/185 (87.6)	81/96 (84.4)	72/84 (85.7)	81/96 (84.4)	81/89 (91.0)
Risk difference (%) (95% CI)	-2.9 (-9.9 to 4.0)		1.4 (-5.6 to 8.3)		-1.3 (-11.8 to 9.1)		-6.6 (-16.0 to 2.8)	
P value	0.41		0.70		0.80		0.17	

Variable	Comparison 1		Comparison 2		Comparison 3		Comparison 4	
Ablation success based on both diagnostic scan and thyroglobulin - no./total no. (%)	182/214 (85.0)	184/207 (88.9)	183/211 (86.7)	183/210 (87.1)	91/108 (84.3)	92/105 (87.6)	91/108 (84.3)	92/102 (90.2)
Risk difference (%) (95% CI)	-3.8 (-10.2 to 2.6)		0.4 (-6.0 to 6.8)		-3.3 (-12.7 to 6.0)		-5.9 (-14.9 to 3.0)	
P value	0.24		0.90		0.48		0.20	

Ablation success rates were 85.0% in the group receiving 30 mCi versus 88.9% in the group receiving 100 mCi. The group that was prepared using rhTSH had a success rate of 87.1%, whereas patients prepared using thyroid hormone withdrawal had a success rate of 86.7%. All 95% confidence intervals for the differences among groups were within ± 10%, indicating non-inferiority. Similar results were found when looking at the subgroups (using the pre-defined comparisons); the success rate for rhTSH + 30 mCi was 84.3%, for rhTSH + 100 mCi it was 90.2%, and for thyroid hormone withdrawal + 100 mCi it was 87.6%.

There was no evidence of an interaction between radioiodine dose and method of preparation (thyrotropin alpha or thyroid hormone withdrawal) on success rates (P = 0.51).

Regarding other important subgroups, analyses of the T3 patients (n = 101) and of patients with neck lymph nodes thought to harbour tumour (n = 70) found that they were successfully ablated with similar rates to other patients. For example, when T3 patients were assessed for ablation success using diagnostic scans alone, the success rates using 30 mCi and 100 mCi were 93.6% and 89.8%, respectively. If both the diagnostic scan and the stimulated Tg level were to be favourable to count for success, then for T3 patients the success rates using 30 mCi and 100 mCi were 80.9% and 81.6%, respectively. If both the diagnostic scan and the stimulated Tg were to be favourable to count for success, then for patients who were both T3 and N1, the success rates using 30 mCi and 100 mCi were 77.8% and 75.0%, respectively. For T3 patients treated with rhTSH versus thyroid hormone withdrawal, the ablation success rates as assessed by scans alone were 89.6% versus 93.8%, respectively. If both the scan and stimulated Tg had to be favourable to count as success, then the success rates for T3 patients treated with rhTSH versus thyroid hormone withdrawal were 83.3% versus 79.2%, respectively.

Logistic-regression analyses indicated that success rates did not differ significantly between the low dose and the high dose on the basis of either tumour stage (P = 0.71 for interaction) or nodal stage (P = 0.27 for interaction).

ESTIMABL Study

The ESTIMABL study (Essai Stimulation Ablation Equivalence Trial; Schlumberger *et al*, 2012) was performed in 24 French centres and compared the same four strategies for thyroid remnant ablation as evaluated in HiLo. Patients in ESTIMABL were, however, TNM stage pT1< 1 cm with N1, or pT1> 1 - 2 cm with either N0 or 1, or pT2 with N0, and for all these patient types there could not be any distant metastases present. Thus, there were no T3 patients included.

684 of the 752 patients enrolled had data that could be evaluated. 79% of patients were female, the mean age was 49 years, and 92% had papillary cancer.

The primary endpoint was the rate of ablation at 8 ± 2 months post-radioiodine therapy, using the assessments of neck ultrasound and rhTSH-stimulated Tg determination (or ^{131}I whole-body scan in

the presence of Tg antibodies).

Patient types were as follows: 30% were pT1N0, 18% were pT1N1, 39% were pT1Nx, and 12% were pT2 N0. In the 684 patients with data at about 8 months that could be evaluated, ultrasonography of the neck showed no thyroid remnant or suspicious neck nodes in 652 (95%), and the rhTSH-stimulated serum Tg level was < 1 ng/mL in 621 of the 652 patients without detectable Tg antibodies. It should be noted that the stimulated Tg cut-off level that defined success was set slightly lower in the French study than in the UK study.

On the basis of the local thyroglobulin determinations, thyroid ablation was judged to be complete in 631 (92%) of the 684 patients. All four treatment arms of the study had very similar ablation rates. For the four groups rhTSH + 30 mCi, rhTSH + 100 mCi, thyroid hormone withdrawal + 30 mCi, and thyroid hormone withdrawal + 100 mCi, the rates of ablation success as judged by neck ultrasound were 97%, 94%, 96% and 95%, respectively, whereas if one judged success by central laboratory stimulated Tg determination the rates of success were 90%, 94%, 93%, and 93%, respectively. Statistically, the four treatments had comparable efficacy.

Equivalence was also shown between the two ^{131}I doses used. There was no interaction between ^{131}I radioactivity and thyrotropin- stimulation method.

2.2.3. Discussion on clinical efficacy

These two well conducted studies, published in a peer reviewed journal, provide appropriate assurance regarding the safety and efficacy of use of lower doses of radioiodine.

There were slight differences in the patients recruited, and in the conduct of the studies, but the basic study designs were the same. The Schlumberger study included only “low risk” patients but the Mallick study included patient with tumour stages T1 to T3, with possible spread to nearby lymph nodes but without metastases.

The Mallick study showed that 30 mCi could be used just as successfully for remnant ablation as 100 mCi, and this also was true in subgroups based on T and N stage. Patients benefited from use of rhTSH, which allowed them to continue thyroid hormone replacement during the ablation procedure, and thereby avoid significant hypothyroidism.

The authors suggested that ‘the efficacy of low-dose radioiodine is similar to that of high-dose radioiodine and that the efficacy of low-dose radioiodine ablation is not compromised by the use of thyrotropin alpha instead of thyroid hormone withdrawal’.

The Schlumberger study similarly showed similar efficacy with high and low dose radioiodine and similar efficacy of thyroid radioablation after preparation with use of either recombinant human thyrotropin or by withholding of thyroid hormone (assessment of ablation was at 8 months).

In comments about their high ablation rates, the authors suggest three reasons: ‘First, a total thyroidectomy was performed in all patients, resulting in small remnants of normal thyroid tissue, as shown by the low uptake of ^{131}I on total-body scan and the low serum thyroglobulin levels at ^{131}I administration. Second, our patients had low-risk disease, with small T1 or T2 thyroid tumours, with no extension beyond the thyroid capsule and no aggressive histologic subtypes. Third, we did not consider the faint uptake in the thyroid bed that is frequently found on control diagnostic ^{131}I total-body scans and that has no clinical importance’.

The authors concluded that, ‘The use of recombinant human thyrotropin and low-dose (1.1 GBq) postoperative radioiodine ablation may be sufficient for the management of low-risk thyroid cancer’.

In the Mallick study, the authors pointed out that their findings relate to 6 and 9 month only and that

long term follow up will be required to examine recurrence rates. In essence, there are no significant long-term data, as the follow up periods in the study were in line with treatment guidelines and current practices for thyroid cancer. Similarly, in the Schlumberger study, the authors note that 'Whether preparation with recombinant human thyrotropin followed by 1.1-GBq ^{131}I radioactivity affects long-term outcomes will be revealed only by following patients over time. However, the currently available data are reassuring in showing that less than 1% of patients with low-risk cancer who had normal neck ultrasonography and an undetectable thyrotropin-stimulated serum thyroglobulin level will have a clinical recurrence over a 10-to-15-year period'.

2.2.4. Conclusions on the clinical efficacy

In conclusion, these two studies provide convincing evidence that supports the proposed SmPC changes. Unless long-term data on recurrence rates using the lower radioiodine dose become available, this lack of information should be described in the SmPC (sections 4.4 and 5.1).

The CHMP considers the following measures necessary to address issues related to efficacy:

Long term data from published investigator sponsored studies studies HiLo and ESTIMABL should be provided when made available.

2.2.5. Clinical Safety aspects

In the HiLo study, the proportions of patients with adverse events during ablation and up to 1 week after the procedure were 21% in the 30 mCi group versus 33% in the 100 mCi group (P=0.007). There was a trend toward fewer adverse events in the rhTSH group (23%) versus in the group undergoing thyroid hormone withdrawal (30%; P=0.11), but there were clear quality of life benefits associated with use of rhTSH before ablation. Moreover, patients who had received 100 mCi were more commonly hospitalised for 3 days than were patients who had received 30 mCi (36.3% vs. 13.0%, P<0.001).

In the ESTIMABL study, symptoms of hypothyroidism and SF-36-documented deterioration of quality of life were worse for patients undergoing withdrawal of thyroid hormone than for patients who received rhTSH. The incidence of salivary problems did not differ significantly among the groups, but lacrimal dysfunction (watery eyes) was more frequent among patients undergoing thyroid hormone withdrawal than among patients receiving rhTSH.

In conclusion, symptoms of hypothyroidism occurred in those treated with thyroid withdrawal. No new safety issues in relation to Thyrogen arose in either of the studies.

2.3. Risk management plan

The EU Risk Management Plan (EU-RMP) has been revised to reflect the proposed changes to the SmPC; the important missing information sections of the Safety Specification and Pharmacovigilance Plans have been updated based on the publications mentioned above. Additional changes have been made to render the document up-to-date.

Table 3: Summary of the risk management plan (deleted wording ~~in strikethrough~~)

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities (routine)
Gastrointestinal Symptoms	Routine: Post-marketing surveillance	Section 4.8 (Undesirable effects) SmPC (Annex 2) derived from the CCSI (Annex 7): The frequency of nausea, vomiting and diarrhoea are tabulated

Constitutional Symptoms	Routine: Post-marketing surveillance	Section 4.8 (Undesirable effects) SmPC (Annex 2) derived from the CCSI (Annex 7): The frequency of headache, fatigue, dizziness and influenza-like illness are tabulated
Injection Site Reactions	Routine: Post-marketing surveillance	Section 4.8 (Undesirable effects) SmPC (Annex 2) Discomfort, pain, pruritus, rash and urticaria at the site of intramuscular injection are tabulated.
Hypersensitivity to Thyrogen	Routine: Post-marketing surveillance	Section 4.3 (Contraindications) SmPC (Annex 2) derived from the CCSI (Annex 7): Hypersensitivity to human thyroid stimulating hormone or to any of the excipients. Section 4.8 (Undesirable Effects) SmPC (Annex 2) derived from the CCSI (Annex 7): 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.
Neoplasm Swelling	Routine: Post-marketing surveillance	Section 4.4 (Special Warnings and Precautions for Use) SmPC (Annex 2) derived from the CCSI (Annex 7): 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. Section 4.8 (undesirable effects) SmPC (Annex 2), includes the following text, in line with text in Section 4.4: 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. A separate cumulative analysis of cases reporting thyroid swelling will be provided in the next PSUR.

Altered Pharmacokinetics in Patients with Advanced or End-Stage Renal Disease	Routine: Post-marketing surveillance	Section 4.2 (Posology and Method of Administration) SmPC (Annex 2) derived from the CCSI (Annex 7): 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.
Medication Errors	Routine: Post-marketing surveillance	Section 4.2 (Posology and Method of Administration) SmPC (Annex 2) derived from the CCSI (Annex 7): The recommended dose regimen is two doses of 0.9 mg thyrotropin alpha administered at a 24-hour interval by intramuscular injection only. Therapy should be supervised by physicians with expertise in thyroid cancer. A separate review of medication errors during the reporting period of the next PSUR will be provided in the next PSUR
Neoplasm Growth (Theoretical)	Routine: Post-marketing surveillance	Section 4.4 (Special Warnings and Precautions for Use) SmPC (Annex 2) derived from the CCSI (Annex 7): There is a theoretical possibility that Thyrogen, like thyroid hormone withdrawal, may lead to stimulated tumour growth. In clinical trials with thyrotropin alpha, which produces a short-term increase in serum TSH levels, no case of tumour growth has been reported
Cardiac Events in Patients with Intact Thyroid (Off-label Use in Goitre Patients)	Routine: Post-marketing surveillance Additional pharmacovigilance activity: A questionnaire has been implemented for all spontaneous reported cases to capture cardiovascular medical history.	Section 4.4 (Special warnings and precautions for use) SmPC (Annex 2) derived from the CCSI (Annex 7): 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 tachyarrhythmias 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. Section 4.8 (Undesirable Effects) SmPC (Annex 2) derived from the CCSI (Annex 7): 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. A separate cumulative analysis of cases reporting cardiovascular adverse reactions will be provided in the next PSUR. The next PSUR will include an evaluation of all cases which are potentially associated with off-label use, tracked by searching by indication as well as alternate dosages of Thyrogen used (i.e., lower doses used for the goitre indication).

Perceived lower TSH elevation after Thyrogen administration	Routine: Post-marketing surveillance	Section 4.2 (Posology and Method of Administration) SmPC (Annex 2) derived from the CCSI (Annex 7): 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.
Anti-TSH antibodies in patients previously exposed to Bovine TSH	Routine: Post-marketing surveillance	Section 4.3 (Contraindications) SmPC (Annex 2) derived from the CCSI (Annex 7): Hypersensitivity to bovine thyroid stimulating hormone Section 4.8 (Undesirable Effects) SmPC (Annex 2) derived from the CCSI (Annex 7): In clinical trials involving 481 patients, no patients have developed antibodies to thyrotropin alpha 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.
Use of Thyrogen in Pregnant or Lactating Women	Routine: Post-marketing surveillance	Section 4.3 (Contraindications) SmPC (Annex 2) Pregnancy Section 4.6 (Pregnancy and Lactation) SmPC (Annex 2) derived from the CCSI (Annex 7): 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, because of the consequent exposure of the foetus to a high dose of radioactive material. Patients should not breast-feed.
Use of Thyrogen and dosing in paediatric patients	Routine: Post-marketing surveillance	Section 4.2 (Posology) SmPC (Annex 2) derived from the CCSI (Annex 7): Due to a lack of data on the use of Thyrogen in children, Thyrogen should be given to children only in exceptional circumstances
~~Use of Thyrogen in remnant ablation using radioiodine activity below 100 mCi~~	~~Routine Post-marketing surveillance~~	~~Section 4.1 (therapeutic indication) SmPC (Annex 2)~~ ~~Use of Thyrogen for remnant ablation is restricted to combination with 100 mCi radioiodine only.~~ ~~Section 4.4 (Special warnings and precautions for use SmPC) (Annex 2)~~ ~~In the pivotal trial of Thyrogen for pre-therapeutic stimulation before radioiodine (^{131}I) ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer, an activity of 100 mCi (3.7 GBq) radioactive iodine (^{131}I) was used. Experience of rhTSH in combination with other radioiodine activities, in particular as low as 1 GBq is very limited. The efficacy of rhTSH for thyroid remnant ablation in combination with low radioiodine activities has not been demonstrated.~~

~~Use of Thyrogen for remnant ablation in patients originally diagnosed with T3NxM0 thyroid cancer~~	~~Routine Post-marketing surveillance~~ ~~Additional activity: Submission of results from investigator sponsored study in the UK ('HiLo'), in particular in relation to patients with T3 thyroid cancer (post approval commitment from variation 38).~~	
Use of Thyrogen for remnant ablation in patients originally diagnosed with T4N0-1M0-1 thyroid cancer	Routine Post-marketing surveillance Additional activity: Submission of a protocol to collect data about remnant ablation in patients originally diagnosed with T4 thyroid cancer (post approval commitment from variation 38).	
Focal Neurologic deficit after Thyrogen administration	Enhanced Post-Marketing surveillance	Update the SmPC Section 4.8 under "Undesirable Effects" to include: "Very rare cases of stroke have been reported from world-wide post marketing experience in female patients. The relationship to Thyrogen administration is unknown."

The CHMP, having considered the data submitted, was of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product.

3. Overall conclusion and impact on the benefit/risk balance

The MAH has proposed the update of the section 4.1 and a number of related amendments to the SmPC to allow the use of lower doses of radioiodine in thyroid ablation. In principle, the use of a reduced dose of radioiodine has important advantages. Patients, many of whom are women with children, would spend less time in hospital isolation and have fewer side effects, especially a reduced risk of a second primary cancer caused by exposure to radioactive substances.

In the United Kingdom, 2007 guidelines recommend the use of high-dose radioiodine. Guidelines of the U.S. National Comprehensive Cancer Network (2010), the American Thyroid Association (2009), and a European consensus report (2006) indicate that clinicians can choose between the low dose and the high dose. However, reliable evidence was lacking.

When the indication for use of Thyrogen for remnant ablation was granted, there was evidence of appropriate efficacy for Thyrogen when used with 100 mCi ^{131}I (3.7 GBq), but only limited data when used with 30 mCi (1.1 GBq) were available. Several relevant publications were inadequate to provide convincing evidence of efficacy.

The recent publication in New England Journal of Medicine of two clinical trials in which use of 30 mCi (1.1 GBq) was compared with use of 100 mCi (3.7GBq) for remnant ablation (preparatory methods of Thyrogen versus thyroid hormone withdrawal also were tested using a 2 x 2 factorial design within a

non-inferiority structure) now provides better evidence of similar efficacy when Thyrogen is used with 30 mCi (Mallick, 2012, N Engl J Med; Schlumberger, 2012, N Engl J Med).

These two, well performed, randomised, prospective studies compared both high and low dose radioiodine and also the two possible strategies for preparation of patients for radioiodine administration. The Schlumberger study included only “low risk” patients but the Mallick study included patient with tumour stages T1 to T3, with possible spread to nearby lymph nodes but without metastases.

The Mallick study concluded that the study had shown that the efficacy of low dose radioiodine was similar to that of high dose radioiodine. Moreover, adverse events were higher and hospitalisations were longer with the higher radioiodine dose, while quality of life was better with the use of recombinant human thyrotropin than with thyroid hormone withdrawal. The authors point out that findings relate to 6 and 9 month only and long term follow up will be required to examine recurrence rates.

The Schlumberger study similarly showed similar efficacy and safety with high and low dose radioiodine and similar efficacy of thyroid radioablation after preparation with use of either recombinant human thyrotropin or by withholding of thyroid hormone (assessment of ablation was at 8 months), while, as expected, safety was better with recombinant human thyrotropin than with thyroid hormone withdrawal.

These two studies provide convincing evidence that supports the agreed SmPC changes. The benefit-risk of Thyrogen when used with a range of ^{131}I dose between 30 mCi (1.1 GBg) and 100 mCi (3.7 GBq) 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, is considered positive.

Moreover, FUM 035 can be considered fulfilled.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of section 4.1 of the SmPC in order to recommend the use of Thyrogen with a range of 30-100 mCi ^{131}I for postoperative thyroid remnant ablation, as opposed to the currently approved 100 mCi ^{131}I, based on the results of two published studies (HiLo and ESTIMABL). Sections 4.4, 4.5 and 5.1 are updated accordingly to amend relevant existing warnings and to include information from the two studies.

In addition, the MAH took the opportunity to make minor editorial amendments in the SmPC and to update the list of local representatives in the Package Leaflet.

Furthermore, the PI is brought in line with the latest QRD template version 8.1.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.