

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Thyrogen and has been updated until 1 July 2004. For information on changes after this date please refer to module 8B.**

### 1. Introduction

Thyroid cancer is an uncommon disease, which affects mostly female adult patients. Well-differentiated thyroid cancer accounts for 80-90% of all thyroid cancers. Initial treatment is total or near-total thyroidectomy. Once the gland has been removed the patient is given thyroid hormone suppression therapy (THST), either thyroxine ( $T_4$ ) or tri-iodothyronine ( $T_3$ ), to suppress thyroid stimulating hormone (TSH) serum levels to below 0.5 mU/l. TSH suppression is necessary to avoid stimulation of thyroid remnants or thyroid cancer. Recurrences and metastases tend to develop slowly, requiring prolonged follow-up.

Thyrogen contains the active ingredient thyrotropin alfa, which is recombinant human thyroid-stimulating hormone (rhTSH). The indication initially approved was use with radioiodine imaging together with serum thyroglobulin (Tg) testing undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on thyroid hormone suppression therapy (THST). Further to the assessment of a type II variation, the indication was extended to include use with or without radioiodine imaging and the possibility of following up low risk patients with well-differentiated thyroid carcinoma who have undetectable Tg levels on THST and no rhTSH-stimulated increase of Tg levels.

Thyrogen is formulated as a powder for solution for injection. The recommended dose regimen is two doses of 0.9-mg thyrotropin alfa administered intramuscularly 24 hours apart. Radioiodine administration is performed 24 hours after the last dose and scanning is performed 48-72 hours later. Serum Tg should be measured 48-72 hours after the last dose.

### 2. Chemical, pharmaceutical and biological aspects

#### Composition

Thyrotropin alfa is human thyroid stimulating hormone produced by recombinant DNA technology. The product is a lyophilised powder presented in a 5-ml glass vial with siliconised butyl stopper. The powder is reconstituted with 1.2 ml of sterile water for injection and 1 ml is withdrawn for a 0.9-mg dose. Preclinical and early clinical trials used a formulation of 3.6 mg/ml but the same dosage of 0.9 mg. Thyrogen is formulated for single use intramuscular injection and as such contains no preservative.

#### Active substance

##### *Description*

Thyrotropin alfa is a heterodimeric glycoprotein produced by recombinant DNA technology. It is a recombinant form of the naturally occurring protein TSH, and is comprised of 2 non-covalently linked subunits, an alpha subunit of 92 amino acid residues containing two N-linked glycosylation sites (asparagine 52 and 78) and a beta subunit of 118 amino acids containing one N-linked glycosylation site (asparagine 23). The dimer structure is essential for function.

Thyrotropin alfa has comparable biochemical properties to natural human TSH. Binding of thyrotropin alfa to TSH receptors on thyroid epithelial cells stimulates iodine uptake and organification, synthesis and secretion of  $T_g$ ,  $T_3$  and  $T_4$ .

The ATC code for thyrotropin alfa is V04CJ01.

Comprehensive structural analysis of thyrotropin alfa has been performed to investigate the primary, secondary, and tertiary structure, and post-translational modifications. The aim of thorough structural analysis was to prove authenticity with human pituitary TSH (phTSH). The primary sequences of both proteins were comparable.

### Cell bank

Thyrogen is produced by mammalian cell culture using a Chinese Hamster ovary (CHO) cell line co-transfected with recombinant plasmids containing DNA sequences encoding the alpha and beta subunits of TSH. A stable subcloned cell line expressing TSH was used to prepare a master cell bank (MCB) that was tested for bacterial, mycoplasmal, fungal and viral agents.

The MCB has been fully characterised, as were EOP (End of Production) cells. Results were typical for a cell substrate of Chinese Hamster origin. The cells should be considered as being tumourigenic. There was no evidence of fungal, bacterial or mycoplasmal contamination. No viral particles apart from intracytoplasmic A-type particles were detected. A battery of *in vitro* and *in vivo* tests were negative for infective, endogenous or adventitious viruses.

### Fermentation

Production of the active ingredient is performed by Genzyme, Framingham, Massachusetts, USA. The protein is produced by a batch-harvest/re-feed type fermentation using cells from the Working Cell Bank (WCB), which is derived from the MCB.

Comprehensive details on fermentation conditions, raw materials and growth media used in cell culture were provided. All materials of animal origin comply with the CPMP/BWP/877/96 note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products and EMEA 354/96 opinion of the EMEA on the potential risk associated with medicinal products in relation to Bovine Spongiform Encephalopathy (BSE).

Adequate In Process Controls are performed. Harvests are stored in dedicated containers until further processing. The suitability of these holding conditions has been confirmed.

### Purification

Bioreactor harvests meeting specifications are filtered, pooled, concentrated by ultrafiltration, diluted and purified by several column chromatography steps utilising several modes of separation, before being concentrated, diafiltered and diluted to a target concentration (unformulated purified bulk). Full details on reagents, column sanitisation and qualification have been provided. Storage times and conditions of the intermediates have been satisfactorily validated. In-Process Control testing is conducted on eluate fractions and pools.

### **Product development and finished product**

The finished product is manufactured at the Genzyme facility in Allston, Massachusetts, USA. The 'unformulated purified bulk' is formulated to a final concentration of 0.9 mg/ml and then sterile filtered through a  $\leq 0.22\text{-}\mu\text{m}$  filter, filled into depyrogenated vials, lyophilised, stoppered and packaged. The manufacturing process is described in sufficient detail. The formulated bulk is tested for chemical, physical and microbiological aspects according to the specification provided.

During the assessment, the company submitted a full-scale validation report for the intended commercial scale. This scale was twice as high as that of the initially submitted scale. A GMP inspection was performed at the manufacturing site on March 25 1999 to address a Quality Assurance issue. The corrective steps taken by the company were considered acceptable.

The recommended dosing and administration of thyrotropin alfa is based on protein content rather than activity. The use of a direct spectrophotometric method for determining thyrotropin alfa content has been justified by the high purity of the produced protein (99.9%). An ELISA test is also used to measure the concentration of intact rhTSH dimers for which the Company has tightened the specifications. The only source of non-specificity for this method is interference from dissociated TSH subunits. In view of this, the Company has developed and validated a test method for the determination of these dissociated subunits using native PAGE (polyacrylamide gel electrophoresis). The Company has committed to review the Native PAGE specification when further data become available.

Two bioassays are performed to evaluate the specific activity, both of which are variable. The *in vitro* bioassay is based upon the radioimmunoassay measurement of cyclic adenosine monophosphate (cAMP) produced by a bovine thyroid gland microsome preparation in response to a thyrotropin alfa test sample in comparison with a reference standard curve. The Company has committed to

establishing an in house reference standard when data from further lots will be available. In the meantime the WHO TSH standard is used.

The *in vivo* bioassay is based on TSH-stimulated T<sub>4</sub> secretion in mice with suppressed endogenous TSH levels. The mass of TSH required to obtain a half maximal T<sub>4</sub> response (ED<sub>50</sub>) is calculated from a dose response curve. The Company argued that it is inappropriate to calculate confidence levels for this bioassay's results due to the method format. In addition, the Company has committed to developing and validating a cell-based bioassay, which eventually will replace both the *in vivo* and *in vitro* assay.

Thyrotropin alfa exists as a mixture of isoforms reflecting a variety of post-translational modifications including sialylation, which in turn may influence bioactivity. In order to address the limitations of the bioassays and in order to address the variability in carbohydrate composition, the Company has performed a comparative isoelectric focussing (IEF) study using a rhTSH reference material. This study demonstrated a consistent isoform pattern among several finished product lots. The addition of a comparative IEF test to finished product testing will give reassurance as to the consistency of product manufacture. A specification for sialic acid content has also been added for the finished product. The primary route of degradation observed for the finished product of Thyrogen is aggregation (tested by SEC – HPLC). Other potential modes of degradation for a heterodimeric glycosylated protein include subunit dissociation, deglycosylation, protein fragmentation, deamidation oxidation and denaturation.

The Company provided stability data that support the proposed storage times and conditions.

The Company has limited stability data on full scale (12,000 vials) production batches (2 lots for up to 9 months) but has supporting data on 6,000 vials lots (two lots up to 18 months) and 3,000 vial lots (three lots up to 36 months) which support a shelf-life of 36 months when stored between +2 and +8 C°. Results from the first three production batches will be submitted on an ongoing basis.

#### Viral safety

The chromatography columns are the essential elements of the purification procedure of Thyrogen. Virus clearance potential has been investigated in the chromatography steps. Full details on the scaled down, viral spiking studies on the four relevant chromatographic steps have been provided. Each column chromatography step was evaluated separately with several model viruses. From these data it can be concluded that the combination of the column steps, which represent a broad spectrum of chromatographic separation, provides a considerable potential for virus removal. The viral safety of Thyrogen is sufficiently demonstrated by the extensive test strategy (cell bank system, bioreactor harvest, and biological reagents) for viral contamination and the high capacity of the purification process for virus removal (10 to 12 logs).

#### **Discussion on chemical, pharmaceutical and biological aspects**

Except for a limited number of points, which could be addressed as part of post-authorisation commitments, the chemical, pharmaceutical and biological documentation provided by the Applicant demonstrated the Quality of Thyrogen. These post-authorisation commitments were a critical part of the positive CPMP Opinion issued in July 1999. Failure to provide a satisfactory response to these commitments was deemed to constitute a potential risk to public health as they related to the consistency of manufacture and thereby the Quality of Thyrogen. In October 1999 the Applicant provided satisfactory information and the issues concerning the Quality of the product were resolved.

### **3. Toxicopharmacological aspects**

The pre-clinical study reports submitted in Part III of the dossier were based on the requirements laid down in the International Conference on Harmonisation document «Pre-clinical safety evaluation of biotechnology derived pharmaceuticals» (ICH S6, CPMP/ICH/302/95). The species used represent laboratory animals commonly used in pharmacologic/toxicologic research and were suitable models for the proposed indication. The studies conducted were adequate in number and type to assess the possible toxicological effects of Thyrogen. Pivotal studies conformed to Good Laboratory Practice (GLP).

Both bovine TSH (bTSH) and human pituitary TSH (phTSH) have been used for this indication, but have been withdrawn from the market for safety reasons (adverse reactions and potential viral transmission). The development of rhTSH was based on the known efficacy and therapeutic dose levels established for TSH from these other sources. This approach resulted in a somewhat abbreviated pre-clinical package.

### **Pharmacodynamics and pharmacokinetics**

The pre-clinical development of Thyrogen was based on the premise that rhTSH has the same activity as native TSH and is therefore unlikely to have toxic effects. Thus most of the pre-clinical studies were multi-purpose, combining efficacy and kinetic measurements with observation for adverse effects. The dose ranges tested, routes of administration and testing protocol were based on experience with bTSH and phTSH and were similar to those proposed for man. There was no documented evidence of dose-range studies with TSH from any source, nor were there any studies to directly compare rhTSH with bTSH or phTSH.

The activity of rhTSH was shown *in vitro*, in a mouse bioassay and in monkeys.

There was good reproducibility of performance between lots of rhTSH, however clarification was requested on some inconsistency between the measured and the claimed activity of the product, and the assays used have been improved.

The pharmacological effect was demonstrated in a study with euthyroid rhesus monkeys. This data was limited by the nature of the product and the low numbers of animals used. One pair of animals received a single dose of rhTSH intramuscularly (IM) followed, after 6 hours, by <sup>123</sup>I in saline intravenously (IV). Thyroid uptake of <sup>123</sup>I increased up to 6 hours, and blood T<sub>3</sub> and T<sub>4</sub> increased up to 24 hours post-dose. A second pair of animals received 3 daily doses of rhTSH IM followed, after 20 hours, by <sup>123</sup>I in saline intravenously (IV). Thyroid uptake of <sup>123</sup>I increased up to 20 hours, and blood T<sub>3</sub> and T<sub>4</sub> increased up to 40 hours post-dose.

Exposure increased linearly with dose, strength and number of injections, metabolism was presumed to proceed via breakdown to constituent peptides, clearance was rapid (T<sub>1/2</sub> = 8 hours) and elimination appeared to be renal.

### **Toxicology**

There were no adverse events noted in any of the monkey trials, pathology data were not available. Two rodent toxicity studies were carried out with full pathology, at doses up to 10 times the proposed human dose, with no adverse effects noticed. The results of a bacterial reverse mutation assay with Thyrogen were negative.

Considering the proposed usage and the recommendations of ICH S6, the absence of drug interaction, reproductive toxicity, carcinogenicity and local tolerance studies was considered justified.

Given the proposed usage, there is no short-term toxicological hazard to man.

## **4. Clinical aspects**

The incidence rate of differentiated thyroid carcinomas ranges from 0.5 to 10 cases per 100,000 persons per year (Schlumberger, NEJM, 1998). An increased incidence of papillary carcinomas has been observed in children in areas where nuclear irradiation has occurred (Chernobyl, Marshall Islands). The survival rate at 10 years for middle-aged adults with well-differentiated thyroid carcinomas is above 80%.

In patients with thyroid cancer, a near total or total thyroidectomy is performed and patients are placed on synthetic thyroid hormone supplements to replace endogenous hormone and to suppress serum levels of TSH in order to avoid TSH-stimulated tumour growth. For the optimal diagnosis of thyroid remnants or cancer via radioiodine imaging and Tg testing, a high serum level of TSH is needed to stimulate radioiodine uptake and Tg secretion from thyroid cells. 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. Although less sensitive, it is also common practice to perform Tg testing while patients remain on

thyroid hormones and are euthyroid. With the use of Thyrogen, the TSH stimulation necessary for the diagnostic procedures is achieved while patients are maintained euthyroid on thyroid hormone suppression therapy, thus avoiding the morbidity associated with hypothyroidism.

### **Clinical pharmacology: pharmacokinetics and bioequivalence**

Study TSH94-0301 was designed as a pharmacokinetic and bioequivalence two-arm, randomised, two-way crossover study of two Thyrogen formulations (lot A used for the early clinical studies, and lot B, the formula to be marketed) in patients with well-differentiated thyroid carcinoma.

Arm I received a 0.9 mg IM (intramuscular) injection of lot A (or lot B) and after 14 days a 0.9 mg IM injection of lot B (or A). Arm II received a 0.3 mg IV (intravenous) (or IM) bolus of lot B and after 14 days a 0.3 mg IM (or IV) injection of lot B.

The first arm determined the pharmacokinetic profile of Thyrogen and the bioequivalence of the 2 formulations. Results of the 0.9 mg/ml formulation (lot B, proposed Thyrogen formulation for marketing) indicated that the mean maximum serum TSH (C<sub>max</sub>) was 116±38 (95%CI) mU/l with a mean time to maximum serum concentration (T<sub>max</sub>) of 13±8 hours, a mean elimination half-life (T<sub>1/2</sub>) of 22±8 hours and a mean clearance rate of 36±12 ml/min. No patients from Arm II were included in the analysis because of the intolerance to intravenous Thyrogen. Thyrogen was well tolerated when delivered IM.

### **Clinical efficacy**

Studies: TSH91-0601, TSH92-0601 and TSH95-0101

The 3 studies: TSH91-0601, TSH92-0601 and TSH95-0101 had a similar design to evaluate the within-patient comparison of <sup>131</sup>I imaging and Tg testing following Thyrogen stimulation while continuing THST (referred to as Thyrogen phase) and after THST withdrawal (referred to as Hypothyroid phase). Each study also compared signs and symptoms while patients were clinically euthyroid on Thyrogen with the status after THST withdrawal. Placebo control groups were not used because of ethical considerations regarding modality of testing and each patient served as his own control.

Efficacy endpoints were within-patient comparisons of <sup>131</sup>I uptake observed on whole body scans (WBS) following Thyrogen stimulation and THST withdrawal with measurement of Thyrogen and endogenous TSH-stimulated Tg release as well as comparison of signs and symptoms during the Thyrogen and Hypothyroid phase. WBS was performed 48-72 hours after a diagnostic dose of 2-4 mCi <sup>131</sup>I.

A disease staging system was used to classify <sup>131</sup>I uptake. WBS were evaluated by Independent Reviewers (IR) who were blinded to the sequence of the scans. In addition to the IR evaluation each Principal Investigator (PI) evaluated the scans in an unblinded manner. The unblinded results were not used for study analyses.

All clinical studies employed within-patient comparisons of hypothyroid signs and symptoms using the Billewicz Scale. Quality of Life assessment was made using the Profile of Mood States (POMS) and SF-36, a patient self-administered scale. The Wilcoxon Signed Rank test was used to compare symptoms between baseline and either Thyrogen or Hypothyroid phase within each treatment arm and the Mann-Whitney test was used for between arm comparison.

Two populations were defined for use in the efficacy analyses: Intention-to-Treat (ITT) and Efficacy Evaluable Population (EEP). ITT included all patients who were randomised and who had a baseline and at least one efficacy evaluation after receiving at least one injection of Thyrogen. All analyses were performed on the appropriate ITT population. EEP was used in the analysis of the Uptake classification (within patient comparison of scans) and Uptake classification (between dosing regimen arm comparison). EEP included all patients enrolled except those who failed to meet the criteria for inclusion and exclusion, had inappropriate TSH levels and scan pairs review or did not complete the study. The two-tailed Fisher's Exact test was utilised to test whether discordance favoured the Thyrogen or Hypothyroid phase.

## *Dose response studies and main clinical studies*

### Study TSH91-0601 – safety and dose ranging

This was a multi-centre open label dose ranging study to evaluate the safety and preliminary efficacy of Thyrogen in 19 adults ( $\geq 18$  years) with well differentiated thyroid cancer who had undergone near-total or sub-total thyroidectomy and who were being scanned prior to consideration for  $^{131}\text{I}$  ablation.

Seven IM dosing regimens were evaluated, of which three were effective in stimulating  $^{131}\text{I}$  uptake and retention: administration of a single injection of 0.9 mg, two injections of 0.9 mg 24 hours apart or a single injection of 1.8 mg. Twelve patients had concordant Thyrogen and Hypothyroid Phase scans. Four patients had Thyrogen scans rated better than Hypothyroid phase scans (3 showed additional sites of uptake, 1 had a better visual scan). In 3 patients the Hypothyroid phase scan visualised one additional focus.

The efficacy of Thyrogen in stimulating  $^{131}\text{I}$  uptake into residual and metastatic thyroid tissue was demonstrated in this study. A Thyrogen dosing regimen of 0.9 mg administered in two IM injections 24 hours apart was selected for further investigation in the Phase III studies because it could provide prolonged TSH stimulation, which is an important factor in stimulating uptake in patients with metastatic cancer. It was also well tolerated.

### Study TSH92-0601

This was a multi-centre open label, single arm safety and efficacy study.

A total of 152 patients with well-differentiated thyroid cancer were enrolled and treated with 2 injections of 0.9 mg of Thyrogen 24 hours apart. Nineteen percent of patients were enrolled in the study after a recent thyroidectomy prior to ablation and 81% as part of the follow-up monitoring of their thyroid cancer. There was scan concordance in 116/138 of the Intent-to-treat (ITT) patients (84.1%) and discordance in 22/138 patients (15.9%). When discordant, the prevalence of more sensitive Hypothyroid phase scans ( $n=19$ ) was significantly greater than the prevalence of more sensitive Thyrogen phase scans ( $n=3$ ) ( $p<0.0001$ ). Scan concordance was not influenced by a significant number of concordant negative scans. Sixty-five patients had a positive WBS following either THST withdrawal or Thyrogen administration. Scan concordance in this group was 44/65 (67.7%).

In conclusion, the Thyrogen scan was equivalent to or superior to the Hypothyroid phase scan in 86.2% of patients while the Hypothyroid phase scan was equivalent or superior to the Thyrogen scan in 97.8% ( $p<0.001$ ). While equivalence/superiority was somewhat greater with the Hypothyroid phase scan, using Thyrogen the patient would not be rendered hypothyroid. The increased clearance of  $^{131}\text{I}$  in the euthyroid state may have affected the quality of the WBS during the Thyrogen phase.

Tg testing: in 13 patients who had thyroid cancer confirmed by a WBS conducted after the patient received a therapeutic dose of  $^{131}\text{I}$  the Tg tests performed at baseline during THST was falsely negative ( $<3\text{ng/ml}$ ) in 6 patients. Tg testing after stimulation with Thyrogen produced true positives in only 3 out of these 6 patients. This evaluation of Tg testing must be interpreted with caution because of the small number of patients and the fact that a suboptimal timepoint was used to measure Tg levels.

Hypothyroid symptoms: for all the items of the Billewicz scale, and on the POMS scale, significant paired differences ( $p<0.05$ ) favouring Thyrogen was demonstrated.

### Study TSH95-0101

This was a multi-centre open label randomised 2-arm parallel study.

Two dosing regimens were evaluated. A total of 254 patients with well-differentiated cancer were enrolled in this study and 229 patients were treated with Thyrogen and randomised in one of the 2 dosing regimens: administration of 2 injections of 0.9 mg 24 hours apart (arm I) or 3 injections of 0.9 mg 72 hours apart (arm II).

17% of the patients were enrolled after a recent thyroidectomy prior to ablation and 83% were enrolled as part of the ongoing monitoring of their thyroid cancer. The latter included a subgroup of 49

patients (19 in Arm I and 30 in Arm II) who received therapy for metastatic cancer confirmed by either a Hypothyroid phase Tg value of 10 ng/ml in a successfully radioablated patient, surgical resection of metastatic tissue or a positive Hypothyroid phase of post-therapy scan. Arm II patients had a bigger proportion of patients over 65 years (24% *versus* 8%) and a higher proportional number of patients with positive diagnostic scans and evidence of metastatic disease.

In conclusion, the Thyrogen phase scan was equivalent to or superior to the Hypothyroid phase scan in up to 92.5% of patients. The Hypothyroid phase scan was equivalent to or superior to the Thyrogen phase scan in up to 97% of the patients. Two- and three-dose treatment groups did not differ significantly and there was no significant difference between Thyrogen and Hypothyroid phase scans. A combination of Thyrogen-stimulated WBS and Tg assays detected the presence of thyroid remnant or cancer in 12/13 patients who had discordant WBS favouring the Hypothyroid phase.

As measured by the Billewicz Scale, significant ( $p < 0.05$ ) paired differences were observed for hypothyroid signs and symptoms between the Thyrogen and Hypothyroid Phases. As a secondary objective, data on quality of life (QOL Concept SF 36) were collected, and showed differences in favour of Thyrogen on most items (physical functioning, role-physical, bodily pain, role-emotional, mental health, standardised mental component scale, standardised physical component scale). No significant differences could be shown on general health, vitality and social functioning.

#### *Conclusion on efficacy*

The number of studies performed is small. However, thyroid carcinoma is an uncommon disease and maximum information has been gained from the studies performed. It would have been preferable in the second Phase III study TSH95-0101 if all patients had received the proposed 2-dose regimen. Nevertheless sufficient information was gained.

The initially sought indication was use with radioiodine imaging and/or serum Tg testing undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy. However the CPMP is of the opinion that the sensitivity and specificity of the measurement of Tg (Tg) alone is too low to be helpful in the follow up of thyroid cancer patients. The combination of WBS and Tg testing improves the detection of remnants or residual thyroid cancer and gives the comparable results with WBS after THST withdrawal.

A statement on greater sensitivity of Tg (Tg) testing on Thyrogen than on thyroid hormone suppression therapy (THST) has been included in section 5.1 of the SPC.

It can be concluded that:

- The combination of Thyrogen-stimulated Tg and WBS is for the most part comparable to THST withdrawal in detecting thyroid remnants and cancer.
- There is a general absence of hypothyroid signs and symptoms and better Quality of Life following Thyrogen.

#### **Clinical safety**

Studies: TSH91-0601, TSH92-0601 and TSH95-0101 (as for clinical efficacy)

Safety endpoints for the trials included vital signs, haematological and clinical chemistry testing and testing for the development of antibodies against Thyrogen. The Safety population was defined as all patients who enrolled in the study and received at least one injection of Thyrogen.

Headache was experienced by 37/419 patients (8.8%). Two episodes of headache were described as severe, one of which resolved in 2 hours, the other resolved over 6 days. There was apparently no correlation between the occurrence or the severity of headache and the serum level of TSH. One death, due to pulmonary embolism and thought to be unrelated to Thyrogen administration, occurred during the clinical trials..

In general Thyrogen was well tolerated. Asthenia, dizziness, paresthesia, pain, fever, chills and flu symptoms occurred in less than 5% of 419 patients. A few patients reported symptoms at the injection site consisting of pain, pruritus and maculopapular rash. The most common adverse events experienced by more than 5% of the patients were nausea and headache. Nausea was experienced by 53/419 (12.6%) and was more common in the 2-dose regimen compared to the 3-dose regimen. Two

patients experienced pain at the site of metastatic disease. This pain settled spontaneously. Intravenous administration was poorly tolerated and should be avoided.

At the time of submission of the marketing application, only 27 patients had received two courses of Thyrogen. While none of these have developed antibodies, the possibility of antibody development with multiple courses cannot be excluded. The Company has committed to continue collecting antibody data during marketing, and to test for specific antibodies all patients who experience a reaction suggestive of an immune-mediated aetiology.

Finally, there is a theoretical possibility that Thyrogen, like thyroid hormone withdrawal, may lead to stimulated tumour growth. However, any changes in tumour size reportedly seen with Thyrogen are more likely to be due to oedematous or haemorrhagic changes.

## **5. Overall conclusions and benefit/risk assessment**

### **Benefit/risk assessment**

The data provided to show efficacy - even bearing in mind the limitations due to the small population explored, as this is a rare disease - are sufficient to prove adequacy for use with radioiodine imaging together with serum Tg testing for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy.

The use of Thyrogen avoids the hypothyroidism symptoms which occur during withdrawal of THST, without interfering with the accuracy of radioiodine imaging.

The safety database, although limited, shows good tolerability.

The risk benefit ratio is considered to be favourable in light of the clinical findings.

### **Conclusion**

The Company has provided adequate data to support a Marketing Authorisation for Thyrogen in light of the current scientific knowledge.

On the basis of the above considerations, quality, safety and efficacy have been demonstrated in the indication of use with radioiodine imaging together with serum Tg testing undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on THST.

The Committee for Proprietary Medicinal Products recommends the granting of a Marketing Authorisation for Thyrogen, subject to the pharmaceutical biological-follow-up measures undertaken by the Company.

The approved draft Summary of Product Characteristics, Patient Information Leaflet and labelling are annexed to the Committee opinion.

## **6. Extension of the indication to enable the use of the Thyrogen with or without radioiodine imaging**

### *Rationale*

Recent publications have shown that rhTSH-stimulated Tg measurement is sufficiently sensitive to identify residual disease in patients who have no clinical evidence of residual disease and whose serum Tg levels are undetectable during suppression therapy. In addition to rhTSH stimulated Tg measurements used in combination with a WBS, rhTSH-stimulated Tg measurements could also be applied as a first screening test in order to determine further steps on follow-up and/or treatments.

The proposed change, whilst reflecting current medical practice, harmonises the European indication with that approved in other countries - Thyrogen is authorised in the USA, Puerto Rico, Brazil, Israel and Canada as an adjunctive diagnostic tool for serum Tg testing with or without radioiodine imaging in the follow-up of patients with well-differentiated thyroid cancer. Additionally, this change will minimise exposure to isotopes and reduce the costs of follow-up protocols.



## Clinical aspects

Serum Tg measurement and WBS on withdrawal of THST has been seen as the gold standard for the follow-up of differentiated thyroid cancer patients after thyroidectomy and remnant ablation. However, with the advent of Thyrogen, diagnostic studies can be carried out without withdrawal of THST. Recently the possibility was explored that a rhTSH-stimulated Tg test alone might be sufficiently sensitive to detect residual thyroid carcinoma in thyroid cancer patients with no clinical evidence of disease following total thyroidectomy and radioiodine ablation. The negative predictive value and adequacy of a rhTSH-stimulated Tg  $\leq 2$  ng/ml for follow-up of low risk patients (those with prior negative WBS, without elevated Tg levels on suppression therapy and without clinical or histological evidence of metastatic disease) has also been evaluated. It is important to be aware that 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. A number of clinical studies showing that this is feasible have been published. Following is a summary of such publications; all relate to patients without anti-Tg antibodies with one exception.

*Haugen BR, Pacini F, Reiners C et al. A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. J. Clin. Endocrinol. Metab. 1999; 84 (11):3877-3885.*

Two hundred and twenty patients (141 of whom had evaluable serum Tg levels) undergoing surveillance for recurrent thyroid cancer underwent Tg testing and WBS after stimulation by rhTSH. Subsequently, thyroid hormone withdrawal was performed. Thirty patients had metastatic disease, as detected by withdrawal WBS. A Tg  $\geq 2$  ng/ml was detectable in 30/30 patients after both rhTSH stimulation and withdrawal. The data indicated that a stimulated Tg level  $\geq 2$  ng/ml is a sensitive test for metastases.

*Pacini F, Molinaro E, Lippi F, Castagna MG, Agate L, Ceccarelli C, Taddei D, Elisei R, Capezzone M, Pinchera A. Prediction of disease status by recombinant human TSH-stimulated serum Tg in the postsurgical follow-up of differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2001 Dec;86(12):5686-90.*

A prospective crossover study evaluated 72 patients with treated differentiated thyroid cancer and an undetectable Tg on THST. Each patient had a rhTSH-stimulated Tg test on THST followed by a WBS and Tg test on THST withdrawal. Using a cut-off Tg level of 1.0 ng/ml, the rhTSH-stimulated Tg test was able to detect all 19 cases with local or distant metastases, thus achieving a positive predictive value of 100%.

*Robbins RJ, Thomas Chon J, Fleisher M, Larson SM, Tuttle RM. Is the serum Thyroglobulin response to recombinant human thyrotropin sufficient, by itself, to monitor for residual thyroid carcinoma? J.Clin. Endocrinol. Metab. 2002; 87:3242-3247*

In a retrospective study 366 thyroid cancer patients underwent routine follow-up with rhTSH-stimulated WBS and Tg test. It was found that 76% of patients with a stimulated Tg  $> 2$  ng/ml and 13% of patients with a stimulated Tg  $\leq 2$  ng/ml had evidence of residual disease. The outcome was also analysed for a subset of 109 low risk patients, which excluded patients with elevated Tg levels on THST suppression, known metastatic disease, and clinical or histological evidence of metastatic disease. In the low-risk population 7 patients with residual disease in the regional lymph nodes (detectable by ultrasound scanning) had a Tg  $\leq 2$  ng/ml. In this study the patient population was not adequately assessed for the presence of Tg autoantibodies and it is unknown whether the low stimulated Tg level in these patients is a consequence of this. In addition, all 7 patients had a prior positive diagnostic scan. Hence, the negative predictive value of a rhTSH-stimulated Tg  $\leq 2$  ng/ml was 100% if a prior negative WBS had been included in the definition of the low risk subset.

*Mazzaferri EL, Kloos RT. Is Diagnostic Iodine-131 Scanning with Recombinant Human TSH Useful in the Follow-Up of Differentiated Thyroid Cancer after Thyroid Ablation? J Clin Endocrinol Metab 2002; 87:1490-1498.*

In a second retrospective study 107 patients with differentiated thyroid cancer underwent rhTSH-stimulated Tg and WBS testing 10 months to 35 years after initial thyroidectomy and <sup>131</sup>I ablation. About 50% of these patients were at high risk of tumour recurrence. Eighty-seven patients had serum Tg <2 ng/ml, none of whom had a positive WBS. Eleven patients with rhTSH-stimulated serum Tg levels >2 ng/ml were found to have a persistent tumour but the site was not identified by rhTSH-stimulated WBS. In this study a rhTSH-stimulated serum Tg with a cut-off level of 2 ng/ml had a sensitivity of 100%, a negative predictive value of 100% and a false positive rate of 9%.

*Wartofsky L. Management of low-risk well-differentiated thyroid cancer based only on thyroglobulin measurement after recombinant human thyrotropin. Thyroid 2002; 12:583-590.*

A further retrospective study was reported in 300 patients apparently at low risk of recurrence of thyroid cancer (patients had undergone near-total or total thyroidectomy and remnant ablation between 1 and 10 years before enrolment). Patients with distant metastases, or suspected residual disease were excluded. As expected, patients who initially had a more advanced stage of disease were more likely to display elevations in rhTSH-stimulated Tg, with one third of those with stage III disease displaying elevations in Tg of at least 2 ng/ml. A cut-off value of 1ng/ml in Tg in response to rhTSH was considered as the trigger point for further investigation.

*Pacini F, Capezzone M, Elisei R, Ceccarelli C, Taddei D, and Pinchera A; Diagnostic 131-Iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. J. Clin. Endocrinol. Metab. 2002; 87 (4): 1499-1501.*

and

*Cailleux AF, Baudin E, Travagli JP, Ricard M and Schlumberger M. Is diagnostic Iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? J. Clin. Endocrinol. Metab. 2000; 85 (1):175-178.*

Two retrospective studies were performed on the utility of a diagnostic <sup>131</sup>I WBS in patients with well-differentiated thyroid cancer. The data show that in this fairly large series of >600 patients, diagnostic WBS has not given information that could influence strategy, and might be avoided in patients with undetectable Tg after TSH stimulation.

*Haugen BR, Ridgway EC, McLaughlin B, McDermott MT. Clinical comparison of whole-body radioiodine scan and serum thyroglobulin after stimulation with recombinant human TSH. Thyroid 2002; 12:37-43.*

A recent study has retrospectively compared the sensitivity in detecting metastatic disease of rhTSH-stimulated Tg test with that of rhTSH-stimulated WBS with or without Tg test. Of the 83 patients previously treated with thyroidectomy and ablation, 10 had a positive WBS. Using cut-off values of 2 ng/ml and 5 ng/ml, 25 patients and 13 patients were Tg positive, respectively. Nine patients combined a positive Tg (cut-off 5 ng/ml) with a negative WBS. After further evaluation, 6 of these patients had metastatic disease. The authors concluded that rhTSH-stimulated WBS is of limited utility in many patients with differentiated thyroid cancer however there was a high false positivity for rhTSH-stimulated Tg testing.

*Torlontano M., Crocetti U., D'Aloiso L., Bonfitto N., Di Giorgio A., Modoni S., Valle G., Fruscintè V., Bisceglia M., Filetti S., Schlumberger M., Trischitta V. Serum thyroglobulin and <sup>131</sup>I whole body scan after recombinant human TSH stimulation in the follow-up of low-risk patients with differentiated thyroid cancer. The role for neck ultrasonography. Eur. J. Endocrinol. 2002; accepted for publication.*

Torlontano *et al.* carried out a rhTSH-stimulated Tg test + WBS and a neck ultrasound examination in 99 patients with no uptake outside the thyroid bed on the prior post-ablative WBS. All patients underwent the study at the same period of time within a year after initial treatment. In 6 patients rhTSH-stimulated Tg was >5 ng/ml, and in 15 patients it was >1 ng/ml. The diagnostic WBS was negative in all cases. The ultrasound examination identified lymph node metastases in 4/6 patients with a Tg >5 ng/ml, in 2/15 patients with a Tg between 1 and 5 ng/ml, and in 2/78 patients with a Tg <1 ng/ml.

Wartofsky J. *Using Baseline and Recombinant Human TSH-Stimulated Tg Measurements to Manage Thyroid Cancer without Diagnostic <sup>131</sup>I Scanning.* *J Clin Endocrinol Metab* 2002; 87:1486-1489. Recently, an editorial by Wartofsky has provided the following recommendation regarding the use of rhTSH-stimulated Tg tests to manage thyroid cancer without diagnostic WBS.

- diagnostic scanning need not be done when serum Tg on THST is clearly elevated (>2 ng/ml). In this case therapy and a post-treatment scan should be considered.
- diagnostic scanning may be eliminated in those patients with serum Tg on THST < 0.5ng/ml, after initial therapy.
- patients with no clinical evidence of disease who have a Tg on THST of 0.5-2 ng/ml may be followed-up with a rhTSH-stimulated Tg in combination with ultrasound scanning of the neck. If the stimulated Tg is negative and the neck ultrasound is normal these patients may safely be followed by monitoring Tg levels on THST, clinical examination, and ultrasound.

### Discussion and conclusions

There are some limitations to the use of Tg measurements, since anti-Tg antibodies can interfere with accurate serum Tg measurements and Tg results from different assays and laboratories may not be readily comparable. In addition repeated <sup>131</sup>I treatments may cause some thyroid cancer cells to lose the ability to excrete Tg. Notwithstanding these limitations, prospective and retrospective studies indicate that a rhTSH-stimulated Tg test has adequate sensitivity to detect residual or metastatic disease, and that WBS does not add significant information in most patients.

References summarise the results of previous studies investigating the diagnostic value of rhTSH Tg and/or scans in post-thyroidectomy patients with well-differentiated thyroid cancer and proposes an algorithmic approach to the management of such patients based on baseline Tg levels (on suppression) and rhTSH stimulated Tg. This algorithm refers to *low risk patients with well-differentiated thyroid carcinoma* only and suggests that patients with baseline Tg < 0.5 ng/ml and rhTSH-stimulated increase in Tg of < 1 ng/ml may be followed by rhTSH alone. However, for patients with baseline Tg of 0.5-2 ng/ml an additional scan is proposed. Since there is no consensus on this issue and <sup>131</sup>I scan is still considered the diagnostic gold standard, the following statement has been included in section 4.1 of the SPC:

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