Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Thiamazol Henning, Thyrozol (Thiamazole)

DK/W/010/pdWS/001

Rapporteur:	DK
Finalisation procedure (day 120):	25 August 2011
Date of finalisation of PAR	21 October 2011

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section X
INN (or common name) of the active substance(s):	Thiamazole
MAH (s):	See section X
Pharmaco-therapeutic group (ATC Code):	H03BB02
Pharmaceutical form(s) and strength(s):	See section X

I. EXECUTIVE SUMMARY

SmPC changes are proposed in sections 4.2, 4.5 and 4.8.

II. RECOMMENDATION[1]

Based on the review of the presented paediatric data it is recommended that all thiamazole containing products across the EU should include the following wordings in the SmPC:

SmPC section 4.2

Paediatric population
Use in children and adolescents (3 to 17 years of age)
Initial dosage for the treatment of children and adolescents above 3 years of age should be adjusted to the body weight of the patients. Usually treatment is initiated at a daily dose of 0.5 mg/kg, divided into two or three equal doses. For maintenance therapy, the daily dose can be reduced depending on the response of the patient to the treatment. Additional treatment with levothyroxine may be required to avoid hypothyroidism.
A total daily dose of 40 mg thiamazole should not be exceeded.

Use in children (2 years of age and under)
Safety and efficacy of thiamazole in children below 2 year of ages have not been evaluated systematically. Use of thiamazole in children below two years of age is therefore not recommended.

SmPC section 4.5
"Interaction studies have not been performed in paediatric patients"

SmPC section 4.8

Paediatric population
Frequency, type and severity of adverse reactions in children appear to be comparable with those in adults. Severe cutaneous hypersensitivity reactions have been reported in both adult and paediatric patients, including Stevens-Johnson syndrome (very rare including isolated reports: severe forms, including generalised dermatitis, have only been described in isolated cases).

Type IB variation (C.I.3 a) to update sections 4.2, 4.5 and 4.8 of the SmPC and the appropriate sections of the PL to be requested from the MAH by 24 October 2011.

[1] *The recommendation from section V can be copied in this section.*

III. INTRODUCTION

Thiamazole (syn: methimazole) is a sulfur-containing imidazole derivative used as antithyroid drug /thyreostatic, and belongs to the thioamide group (ATC code: H03BB02). Thiamazole is indicated in clinical practice to treat hyperthyroidism. It may also be taken before thyroid surgery to lower thyroid hormone levels and minimize the effects of thyroid manipulation as well as in radioisotope therapy.

Thiamazole is marketed by Sanofi-Aventis Deutschland GmbH as Thiamazol Henning and by Merck KGaA as Thyrozol.

Thiamazole is subject of a Worksharing Procedure according to EC Regulation 1901/2006 ('Paediatric Regulation').
Sanofi-Aventis Deutschland GmbH and Merck KGaA submitted respectively 23 and 8 completed paediatric studies for Thiamazole, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

Short critical expert overviews have also been provided

Merck KGaA stated that the submitted paediatric studies do not influence the benefit risk for Thiamazole and that there is no consequential regulatory action.
In contrast Sanofi-Aventis Deutschland GmbH proposes the following regulatory action: addition of wording regarding the paediatric population to SPC section 4.2, 4.5, 4.8 and 5.2.

Section 4.2:

Proposed new wording to add:

Padiatric population
Use in children and adolescents (3 to 17 years of age)
Initial dosage for the treatment of children and adolescents above 3 years of age should be adjusted to the body weight of the patients. Usually treatment is initiated at a daily dose of 0.5 mg/kg, divided into two or three equal doses. For maintenance therapy, the daily dose can be reduced depending on the response of the patient to the treatment.

Use in children (under 2 year of age)
Safety and efficacy of thiamazole in children below 2 year of ages have not been evaluated systematically. Use of thiamazole in children below two years of age is therefore not recommended.

Section 4.5:

Current wording in PI:

Interaction with other medicinal products and other forms of interaction
Iodine deficiency increases the thyroid's response to thiamazole, whilst iodine excess lowers its response. Further direct interactions with other medicines are not known.
However, it should be taken into account that the metabolism and elimination of other medicines can be accelerated in hyperthyroidism. These normalise in correlation with increasing normalisation of thyroid function. Dose adjustments should be made where necessary.

Proposed new wording***:***

Paediatric population
Interaction studies have not been performed in paediatric patients.

Section 4.8

Current wording in PI:

Undesirable effects
Some of the following side effects associated with thiamazole are also known to be possible symptoms of hyperthyroidism or changes in thyroid function status respectively – particularly hair loss, psychosis, leukopenia, thrombocytopenia, joint and muscle pains and elevated alkaline phosphatase. It is therefore often difficult to determine the cause of onset of any of these symptoms (drug-related side effect or the disease itself).

The following definitions of frequency are used in evaluating undesirable effects:
Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1000 to < 1/100
Rare ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000, including isolated cases

<u>Haematological disorders</u>
Uncommon:
Agranulocytosis occurs in about 0.3-0.6% of cases. It can still become manifest weeks or months after initiation of therapy and may make discontinuation of treatment necessary.
In most cases, agranulocytosis recedes spontaneously. In light of recent knowledge, the granulocyte colony-stimulating factor (G-CSF, filgrastim) would appear to be suitable for the treatment of drug-induced agranulocytosis. However, the approval of a haematologist must be sought before such factors are used.

Very rare including isolated reports:
Isolated reports: thrombopenia, pancytopenia.

<u>Disorders of the skin and appendages</u>
Very common:
Allergic skin reactions (pruritus, exanthema, urticaria) of varying degrees. Such reactions usually run a mild course and frequently recede even with continued therapy.

Very rare including isolated reports:
Severe forms, including generalised dermatitis, have only been described in isolated cases.
Isolated reports: hair loss, drug-induced lupus erythematosus.

<u>Hepatobiliary disorders</u>
Very rare including isolated reports:
Isolated reports of cholestatic jaundice or toxic hepatitis have been described. Such symptoms generally recede upon discontinuation of treatment. Clinically inapparent signs of cholestasis during treatment are to be differentiated from serum GGT activity which was already elevated prior to the start of therapy as a sign of enzyme induction due to hyperthyroidism and as well as of elevated alkaline phosphatase or its bone isoenzyme.

Disturbances in thyroid function
Excess dosage can result in subclinical or clinical hypothyroidism and goitre growth due to TSH increase. Therefore, the Thiamazol Henning dose should be reduced as soon as normal thyroid metabolism is achieved, and/or levothyroxine sodium should be given as an adjuvant. It is not expedient to discontinue Thiamazol Henning altogether and continue treatment with thyroid hormones only.
Goitre growth during Thiamazol Henning therapy where TSH is suppressed, should be regarded as a consequence of the underlying disease that cannot be prevented by adjuvant thyroid hormone therapy.
In a small percentage of cases, late hypothyroidism also occurs during antithyroid monotherapy. This is probably not an adverse drug reaction, but rather the result of inflammatory and destructive processes occurring in the thyroid parenchyma, within the context of the underlying disease.

Eye disorders
For the most part, onset or deterioration of Graves' ophthalmopathy (Thyroid-associated ophthalmopathy) is largely independent of the thyroid disease progression. Such a complication in itself constitutes no grounds for changing the treatment regimen (antithyroid agents, surgery, radioiodine) and should not be regarded as an adverse reaction to correctly performed therapy.

Other undesirable effects
Uncommon:
Drug fever, oedema, taste disturbances (dysgeusia, ageusia) or altered sense of smell. These are reversible upon discontinuation of treatment, whereby normalisation can take up to several weeks.

Very rare including isolated reports:
There have been isolated reports of arthralgia and myalgia, the development of which is generally gradual and which occurs after several months of treatment. There are no clinical signs of joint inflammation.
The following isolated cases have been described: generalised lymphadenopathy, arthritis, nephritis, acute swelling of the salivary glands, vasculitis, neuritis, polyneuropathies and insulin autoimmune syndrome (with a sharp drop in blood sugar values).
All the above-mentioned adverse reactions are probably dose-dependent and therefore occur primarily in the first few weeks of treatment.
By reducing the pathologically increased energy consumption associated with hyperthyroidism, treatment with Thiamazol Henning may induce (a generally desirable) weight gain. Patients should be informed that energy consumption stabilises as the clinical picture improves.

Proposed new wording:

Paediatric population
Frequency, type and severity of adverse reactions in children appear to be comparable with those in adults. Severe cutaneous hypersensitivity reactions reported in both adult and paediatric patients, namely Stevens-Johnsons syndrome, are already implicitely labeled (“Very rare including isolated reports: Severe forms, including generalised dermatitis, have only been described in isolated cases.”).

Section 5.2

Current wording in PI:

5.2 Pharmacokinetic properties
Following oral administration, peak serum concentrations of thiamazole are reached after 1 - 3 hours. Absorption is virtually complete. Despite its relatively short plasma half-life, estimated by various researchers to be between 2 and 8 hours, the antithyroid effect of thiamazole lasts for about 24 hours. This can be attributed to the fact that the substance is actively absorbed into the thyroid gland and that the inhibition of the hormone production evidently correlates to the intrathyroidal concentration and not to the serum concentration. When administered at 8-hour intervals, steady-state thiamazole concentration is achieved in the thyroid after just three single doses, irrespective of the fluctuating serum concentration. There is probably a concentration threshold for the active uptake of thiamazole, which, even at higher doses, cannot be exceeded.
For the most part, thiamazole metabolites are renally excreted with small quantities being excreted in the bile (an enterohepatic circulation exists). 70% of the 14C thiamazole activity can be detected in the urine after 24 hours. After 48 hours, this rises to 80-90%.
A bioavailability study on Thiamazol 20 mg Henning was performed in 1989. Following oral ingestion of one Thiamazol 20 mg Henning tablet on an empty stomach, a serum concentration of 107 ± 70 ng/mL was observed after 15 minutes. The time between tablet ingestion and onset of enteral resorption (lag time) was estimated to be 17 ± 3 minutes. A peak serum concentration of 545 ± 70 ng/mL was reached after 60 minutes. After two hours, the elimination phase was observed, with a half-life of 5.41 ± 0.48 hours.
After 10 hours, serum concentrations of 172 ± 18 ng/mL were only approximately 30% of the maximum concentration. Absolute bioavailability was identified as being 76.55 ± 10.41%, which was slightly higher (although not significantly so) than that of a commercially available control preparation. The following diagram plots the course of mean serum levels following ingestion of Thiamazol 20 mg Henning (n = 12):

Proposed new wording:

Paediatric population
A pharmacokinetic study on thiamazole as single dose was conducted in paediatric patients with Gaucher disease in 1987. Patients received a single oral dose of 20 mg/m^2 (175 µmol/m^2) of body surface area 30 min before breakfast: 20 mg/m^2 (175 µmol/m^2) of body surface area. Plasma levels of thiamazole showed peak concentrations of 4.4 to 12.6 (median 9.2) µmol/l at 0.5 to 4 h after drug administration. Plasma half life ranged from 2.73 to 6.04h. The area under the curve was defined as 32.8 to 77.9 µmol-l^{-1}. h^{-1}, and the distribution volume was between 0.516 and 0.915 l/kg.
Similar to adults, an active absorption of thiamazole into the thyroid gland was observe in paediatric patients.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Thiamazole (syn: methimazole) is a sulfur-containing imidazole derivative used as antithyroid drug /thyreostatic, and belongs to the thioamide group (ATC code: H03BB02). Thiamazole is indicated in clinical practice to treat hyperthyroidism. It may also be taken before thyroid surgery to lower thyroid hormone levels and minimize the effects of thyroid manipulation as well as in radioisotope therapy.
Thiamazole is marketed by Sanofi-Aventis Deutschland GmbH as Thiamazol Henning and by Merck KGaA as Thyrozol.

IV.2 Non-clinical aspects

No relevant published non-clinical trials have been identified

IV.3 Clinical aspects

Merck KGaA performed a literature research in MEDLINE'60 and EMBASE'74, and DERWENT DRUG revealing a total of 3 relevant not yet submitted publications providing data on the use of thiamazole in children.

Sanofi-Aventis Deutschland performed a literature research in 32 public databases for publications of clinical data on thiamazole with specific relevance for the use of thiamazole in paediatric patients. In total, the search identified: 1 open prospective randomized multicenter trial, 13 retrospective studies, 1 study on paediatric pharmacokinetics, 3 reviews of current treatment practice, 2 general reviews and 1 other study.

2. Clinical studyies

From Merck KGaA:

Mora et al. 1999
This study measured spinal and whole body BMD by dual-energy X-ray absorptiometry in a group of 13 girls (aged 5.0–14.9 years) at diagnosis of hyperthyroidism. The patients were studied longitudinally during treatment. BMD values and NTX urine concentrations was also determined in 155 healthy Caucasian girls (aged 2.4–24.2 years). Spinal and whole body bone density measurements were significantly lower compared with healthy controls in untreated hyperthyroid girls, after correction for differences in age and anthropometric measurements (p £ 0.033). Bone density measurements obtained after 12 and 24 months of treatment were no longer different from those of healthy girls. NTX urine levels at diagnosis of thyrotoxicosis were significantly higher than those found in healthy controls ($p < 0.0001$); 6 months after treatment, the urine levels did not show significant differences, and they remained stable after 12 and 24 months of therapy. Inverse correlations at diagnosis were found between serum-free thyroxine (FT4) serum levels and spinal ($r = –0.42$) and whole body bone density ($r = –0.41$); FT4 and free triiodothyronine serum levels directly correlated with the NTX concentration ($r = 0.77$, and $r = 0.71$, respectively). In conclusion, low bone density values and high bone resorption rates are found in hyperthyroid children and adolescents at diagnosis of the disease. Antithyroid treatment is able to reduce dramatically the bone resorption and to increase significantly both spinal and

total body BMD, granting physiologic conditions for the achievement of the best obtainable peak bone mass.

Schendekehl et al 1997
This is an abstract in german and will not be assessed.

Van Santen et al. 2003
In this prospective cohort study, 34 children with neuroblastoma who received MIBG were given thyroxine, methimazole, and potassium iodide for protection of the thyroid gland. Protection started 1 day before the start of diagnostic 123I-MIBG and was continued until 4 weeks after the last therapeutic 131I-MIBG dose. Follow-up measurements were performed every 3 months after the protection was stopped. Visualization of the thyroid on MIBG images was reviewed by three nuclear medicine physicians. Results were compared with a historic control group of children who had received potassium iodide for thyroid protection during MIBG administration. After a mean follow-up of 19 months, there were 23 evaluable patients. Thyroid function was normal in 86% of survivors compared with 44% of children in the historic control group (*P* _ 0.011; Pearson chi-square test). Scintigraphic visualization of the thyroid diminished substantially after the new protection (21.5% vs. 5.3%, respectively; *P* _ 0.000). Thus compared with potassium iodide alone, combined thyroxine, methimazole, and potassium iodide protect the thyroid more effectively against radiation damage from 123/131I during diagnostic and therapeutic MIBG administration in children with neuroblastoma.

From Sanofi-Aventis:

Studies of relevance for the suggested new wordings in the SPC:

Reinwein et al. (1993)
This was an open, prospective randomized multicenter study, in which the effects of increasing the daily dose of antithyroid drugs on long term remission rates were evaluated. The study included 509 patients ≥ 16 years with hyperthyroidism due to GD (mean: 42.7 years in lowdose and 2.1 years in high-dose group). Adolescent patients (aged 16 and 17 years inclusive) were not analyzed separately. Two study groups received either 10 or 40 mg TMZ daily as constant dose throughout the 12-month treatment period (follow-up of 12 months in addition). Levothyroxine was added as needed. Of 309 patients that were evaluated at the end of the study, 63.4% achieved remission of GD. No significant difference in remission rate between low (10 mg/day) and high (40 mg/day) dose TMZ treatment was observed. With 10 mg TMZ daily, 68.4% of the patients were euthyroid after 3 weeks, and 84% after 6 weeks, compared to 83.1% and 91.6% respectively, with 40 mg TMZ daily. No difference was observed in the time interval between treatment cessation and relapse. The rate of AEs was different (P= 0.0038) with 15.5% in the 10 mg/day group and 26.5% in the 40 mg/day group. Main reported adverse events were pruritus, rash, and haematologic events (granulocytopenia, agranulocytosis, pancytopenia; n=1 case each).

Barrio et al. (2005)
A 5-year medical ATD protocol was completed in 20 paediatric patients (18 girls, 2 boys; mean age: 12.1 ± 3.9 y [range: 3.5 to 18 y]). The starting dose of TMZ was 30 mg daily (divided into three doses), except for young children, who received 1 mg/kg daily. Once euthyroidism was achieved, the ATD dose was adjusted to maintain clinical and biochemical euthyroidism (generally reducing the dosage from half to 2/3 of the starting dose, given once daily), with the addition of levothyroxine (LT4, 100 pg) in seven patients. The mean treatment duration was 4 years, the average follow up time was 13.8 ± 5.5 years (range: 5.2 - 22.3 y). In case high doses

of ATD were needed to maintain euthyroidism and TSI was positive after 5 years of treatment, an alternative therapeutic option was recommended. All patients received ATD as the first therapeutic option and achieved euthyroidism after a mean treatment duration of 1.2 months. In seven patients, ATD were discontinued after 2 years of treatment and, since all of those patients relapsed, study was continued with an extended treatment protocol. Eight patients (57.1% of the remission group) reached long-term remission (40% of 20 patients) following a mean treatment duration of 5.4 ± 1.4 years. All patients who required low ATD doses to maintain euthyroidism achieved remission. In contrast, all patients requiring high-maintenance ATD doses failed to remit. Remission rates were higher in pre-pubertal compared to pubertal patients: 66.7% versus 35.3% reached long-term remission with ATD after an average of 6.5 ± 1.6 years and 5.6 ± 2.7 years of ATD treatment, respectively. Minor side effects after ATD were observed in six patients (30%). The most common toxic effect was skin rash (n=6 patients). Other minor reactions included arthralgia and myalgia (n=4 patients), and granulocytopenia and oral aphtas (n=10 patients).

Collen et al. (1980)

This was a retrospective study to determine the clinical course of GD in a paediatric population in which ATD were used as the primary therapeutic modality and continued until sustained remission was achieved.
65 patients from one center and at an age ranging from 7 months to 19 years (mean: 11.6 y) were included. The observation period ranged from 3 months to 16 years. Patients with a body weight of more than 38 kg usually started on 10 mg TMZ tid, while smaller patients usually received 5 mg TMZ tid. Usual initial dose of PTU was 100mg tid. Dosage was subsequently adjusted based on clinical response, leading to a switch to twice-daily dosing in most cases. 55% of the total number of patients received TMZ or PTU alone. Of those, 31 (56%) have undergone remission. Remission appears to occur later in patients > 13 years of age compared to younger patients. Few side effects were observed; most common was urticarial rash within the first weeks after institution of drug; three patients developed migratory polyarthralgia. Resolution of side effects occurred with discontinuation of the drug.

Lazar et al. (2000)

The retrospective study included 40 children with GD treated with ATD in one center. Three different age groups were defined: re-pubertal group: 7 patients (Tanner stage 1) (6.4 ±2.4 y). Pubertal group: 21 patients (Tanner stage 2-4) (12.5 ± 1.1 y). Post-pubertal group: 12 patients (Tanner stage 5) (16.2 ±0.84 y). The patients received either PTU (n=28 patients, 70%) or TMZ (n=12 patients, 30%). TMZ therapy was started at a mean dose of 0.74 ± 0.2 mg/kg daily. In addition, adrenergic blockers (propranolol) were administered to 65% of the patients for 6–8 weeks. After biochemical euthyroidism was achieved, ATD dose was adjusted to maintain clinical and biochemical euthyroid state. All patients became biochemically euthyroid (TT3 < 2.7 nmol/L) within 6–12 weeks from initiation of ATD therapy. Remission was achieved in 10 of the patients receiving ATD (28%) after 3.7 years (±1.1 y) of treatment. Remission occurred in only 10% of the boys compared with 35% of the girls, although this observation did not reach statistical significance. AEs occurred in 35% of patients within the first 24 weeks: Major Aes (agranulocytosis and severe toxic hepatitis) occurred in 2/40 (5%) of the patients. Minor AEs (fever, rash, arthralgia, transient leukopenia, moderate increase in liver enzymes) occurred in 12/40 (30%) of the patients. Group I (prepubertal) tended to have a higher rate of side effects than groups II and III: 71% vs. 28% and 25%, respectively. Their side effects were also more severe.

Mussa et al. (1999)

The study aimed at the identification of factors predictive of lasting remission present at onset.

The 17 patients (2 boys, 15 girls) had a minimum duration of 2 years of treatment with TMZ, plus a minimum follow up time ≥ 3 years. The mean age at diagnosis was 10 ± 2 years and 9 ± 9months. The initial dose of TMZ was set at 0.3 to 0.7 mg/kg daily, and slowly reduced until euthyroidism was established. Typically, lasting remission was achieved at treatment periods beyond 2 years. An initial TMZ dose of 0.3 to 0.7 mg/kg daily was effective in 10/17 patients. A generally better response was observed in children over 11 years. fT3 and fT4 concentration was highest in group with poor outcome and lowest in group who reached a lasting remission after a single course. TRAb (TBIAb) levels at onset were the only factor significantly correlated with the response to treatment. No substantial side effects noted during the study.

Rivkees and Szarfman (2010)

The study is based on the analysis of all adverse events reported in the U.S. FDA´s AE Reporting System (AERS). Aalysis revealed a total of 651 reports for PTU and 822 for TMZ across all age groups. There were more reports for TMZ, except for the youngest age group (< 17 y). For patients < 17 y, 81 reports were identified for PTU and 46 reports for TMZ.
The EBGM values for propylthiouracil in the age group of less than 17 years and in the overall analysis in all age groups were for vasculitis events, with several EBGM values for vasculitis events greater than 50 times higher than expected. These problems included antineutrophil cytoplasmic antibody-positive, leukocytoclastic vasculitis, glomerulonephritis, and other forms of vasculitis. Either these events were reported only with propylthiouracil or EBGM values were higher for propylthiouracil than for thiamazole. When hepatotoxicity was examined in children and adolescents, major differences in the number and proportion of severe liver injury reports for PTU versus TMZ were observed. 23 cases of severe liver injury were observed in the age group below 17 years with PTU; no cases were seen with TMZ. When mild liver injury was examined in children and adolescents, mild liver injury in the under 17-year age group was observed in four children and adolescents treated with PTU and in one child treated with TMZ.
When data were examined using the multi-item gamma-Poisson shrinker (MGPS) across age groups, the EBGM values for severe liver injury with PTU were higher in younger (< 17 y) than older individuals (≥ 17 y). Side-by-side comparison for severe liver injury adverse events for all age groups showed them to be more frequent with PTU than with TMZ. Side-by-side comparison for mild liverinjury for all age groups showed them to be more frequent with TMZ than with PTU.

Rivkees et al. (2010)

This retrospective study of patient records analysed the adverse events that occurred in 100 consecutive paediatric patients with GD when treated with TMZ.The range in the patient age was 3.5 to 18 years (mean 13.2 ± 3.5 y). The patients were treated with an average daily dose of TMZ of 0.3 ± 0.2 mg/kg daily. Medication was given once a day in 60% of patients and twice daily in 40% of patients. Adverse events attributed to the use of the medication were seen in 19 patients at 17 ± 7 weeks of therapy. Whereas most of the adverse events associated with TMZ occurred within the first half year of the treatment onset, some adverse events were observed after one and a half years of therapy in three children. The most common side effects included pruritus and hives (8 patients), diffuse arthralgia, muscle pain, and/or joint pain (5 patients), lymphopenia and esoinophilia (one patient). neutropenia (2 patients) , Stevens-Johnson syndrome with diffuse cutaneous eruption and mucous membrane (3 patients), Mild liver injury (1 patient).

Shulman et al. (1997)

This retrospective chart review compared the clinical and biochemical findings at first evaluation for hyperthyroism in prepubertal and adolescent subjects and their response to treatment. The patient population consisted of 100 children and adolescents (19 boys, 81 girls) at an age of 3.2 years to 20 years at first contact. Patients were subdivided into two subgroups: pre-pubertal (PREPUB) and pubertal (PUB) groups according to Tanner staging. Patients with first-line TMZ

treatment received an initial dose of 0.7 mg/kg/day tid; which was reduced later to individual maintenance dose continued for at least 2 years. At diagnosis, PREPUB patients had significantly longer duration of symptoms and higher serum T3 concentrations compared to PUB group. Average total length of treatment was significantly longer in PREPUB group (3.5 ± 2.9 y) than in PUB group (2.2 ±1.8 y). Seventeen percent of PREPUB treated 5.9 ± 2.8 years (at least 6 months) compared with 30% of PUB treated 2.8 ± 1.1 years achieved at least a 1-year remission after stopping therapy ($p < .01$ for percentage between groups; $p < .05$ for duration of therapy). Thirteen percent of PREPUB children treated 5.4 ± 2.9 years and 22% of PUB subjects treated 2.8 ± 1.1 years achieved a remission of 2 years or longer ($p < .01$ for percentage between groups; $p < .05$ for duration of therapy

Slyper et al. (2005)

In order to evaluate the optimal initial dose of TMZ in paediatric GD patients, a retrospective chart analysis on 45 patients aged 5 to 17 years diagnosed with moderate to severe hyperthyroidism due to GD was conducted. The patients were divided into two groups based on the initial dose of TMZ received: The "low dose" group received < 0.5 mg/kg/day, while the "high dose" group started treatment on a dose of > 0.5 mg/kg/day ("high dose"). The low dose regimen was effective in 42% of the low dose group. In the high dose group, treatment was effective in 82% of the patients. Patients commenced on <0.5 mg/kg/day of TMZ have on average free T4 levels that stay higher for three times longer as those on >0.5 mg/kg/day.
No significant difference in time to escape from TSH suppression between the two regimens was detected.

Ward et al. (1999)

This retrospective review of patient charts evaluated the efficacy of ATD in the initial treatment of paediatric hyperthyroidism and the frequency of use and outcome of radioiodine as second line therapy.The study included 33 children (29 girls, 4 boys) with a mean age of 12.7 years treated in a single center between 1990 and 1994. For the purpose of the analysis, the patients were subdivided into two groups: Patients with ATD therapy only (ATD group), and patients with ATD therapy followed by radiotherapy (ATD+R group). The initial treatment started with PTU (15 patients) or TMZ (18 patients). Initial mean TMZ dose was 0.49 mg/kg/d (SD 0.11) in the ATD group and 0.50 mg/kg/d (SD 0.16) in the ATD+R group. Intended treatment period was 24 month. Addition of propranolol and levothyroxine was allowed if needed. In average, the ATD treatment lasted for 23 (16-30) months in the ATD group and 18 (1-35) months in the ATD+R group Radiotherapy was recommended to 25/33 patients (76%) for the following reasons: adverse effects (3 patients), poorly controlled thyrotoxicosis (8 patients), recurrent hyperthyroidism (13 patients), Recurrent hyperthyroidism occurred at a median of 6 (range 1 to 13) months following cessation of drug therapy. Eight patients (24%) reported side effects of ATD medication, including pruritic eruptions, arthralgias, nausea and vomiting

Dötsch et al. (2000)

This retrospective study of patients chart data was conducted to evaluate the current approach to the management of sustained hyperthyroidism in children and adolescents.
The authors sent a questionnaire to the participating German centres. 56 patients with hyperthyroidism aged 1.1 to 17 years (median 10.5 y) were included in the study. The female/ male ratio was 5 to 1. All patients received ATD treatment as initial therapy. Carbimazole was used in 45% of the patients, smaller subgroups received thiamazole (29%), thiamazole (20%) or propylthiouracil (4%). The average initial dosing was 0.45 (0.09 – 0.83) mg/kg for thiamazole, 0.464 (0.18– 1.24) mg/kg for thiamazole, and 0.55 (0.19-1.1) mg/kg for carbimazole. Initially, all but one patient (98%) achieved euthyroidism. ATD treatment was stopped at different intervals after euthyroidism had been reached (depending on the policy of individual centers). Median duration of antithyroid drug treatment was 23.5 months (range1-84 months). After 2 years, 26/56

(47%) of patients were hyperthyroid or had experienced a relapse. In general, patients were started with a second and, if necessary, with a third course of ATD treatment.

Perrild et al. (1994)

This questionnaire study was initiated to study current European practice in diagnosis and treatment of thyrotoxicosis in childhood. A total of 99 questionnaires were completed. In 98/99 cases ATD treatment was chosen as first line therapy. 83 patients received carbimazole, methimazole or thiamazole (CMT), while 16 patients received PTU as antithyroid drug. No universal agreement on the initial CMT dose was found. Dosing range from 0.25 to 2.0 mg/kg/day, with the majority of patient treated with CMT doses of 0.5 to 1.0 mg/kg/day. In 79% of the cases, the initial treatment was modified on the basis of both clinical and biochemical data. Treatment was continued for a fixed period in 79/99 cases with a median of 1.5 years (range 3 months to > 2 years).

Sato et al. (2007)

Based on a questionnaire study among councilors of the Japanese Society for Pediatric Endocrinology and the Japan Thyroid Association, treatment practice of childhood – onset GD in Japan was described. ATD are used as primary treatment. In 92% of the patients, TMZ was used compared to PTU in 8 % of the cases. The preference for TMZ was justified by greater efficacy, fewer adverse drug reactions and less frequent administration. In general, TMZ is considered safer than PTU, with the exception of pregnancy, as TMZ has been associated with congenital abnormalities.

Okuno et al. (1987)

This study measured TMZ concentration in plasma of paediatric GD patients following a single oral dose of TMZ 30 min before breakfast: 20 mg/m_2 (175 µmol/m_2) of body surface area in nine children and adolescent in thyrotoxic state (age range: 6 to 15y). Blood samples were taken after 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 18, and 24 hours. Plasma levels of TMZ showed peak concentrations of 4.4 to 12.6 (median 9.2) µmol/L at 0.5 to 4 hours after drug administration. Plasma half life ranged from 2.73 to 6.04 hours. The area under the curve was defined as 32.8 to 77.9 µmol/L/h and the distribution volume was between 0.516 and 0.915 L/kg. In addition, the authors studied the intrathyroidal concentrations of TMZ following surgery in 4 adolescents (14 to 17 y) plus 5 adults after thyroidectomy Patients were on continuous TMZ treatment and kept in a euthyroid state for at least 2 weeks prior to surgery (with one exception being still in a thyrotoxic state at the time of surgery). Time from last dose of TMZ to surgery ranged from 5 to 24 hours. TMZ is concentrated in the thyroid gland. The intrathyroidal concentration was maintained for 16 to 24 hours, in spite of short plasma half-life.

V. RAPPORTEUR'S PRELIMINARY OVERALL CONCLUSION AND RECOMMENDATION

Thiamazole is the major ATD in the treatment of hyperthyroidism and the long term use of TMZ is well documented in several retrospective studies examining both efficacy and safety in the paediatric population for 2 years of age into adulthood. The risks to the paediatric population aged 2 to < 18 years of age are assumed to be comparable to the documentation in the adult population. Regarding paediatric patients younger than 2 year, treatment with thiamazole are not recommended due to the lack of data. In most cases antithyroid drug treatment are started once the diagnosis of hyperthyroidism is made. Usually this treatment leads to a normalization of thyroid function within 4 to 6 weeks. The remission rates reported vary between the different studies: From 25% every 2 years to an overall remission after several years of <30 to 40%.

There is very little data on predictors of long-term recurrence in paediatric patients and recommendations for the treatment of hyperthyroidism in the case of relapse are still controversial. Some authors favour the long term application of ATD drugs based on the assumption that, if treatment will be continued long enough, in most cases a stable remission can be achieved, whereas other advocate that ATD treatment should not be continued long-term, as definite remission cannot be expected in more than 30 to 40% of patients. The most relevant initial dosing is also a debate from a fixed starting dose between 10 mg and 40 mg daily to a calculation of the initial dose based on the weight or body surface of the individual patient (0,3-2 mg/kg per day. Of course a certain portion of hyperthyroidism patients will not respond to TMZ therapy and will require other treatment. Regarding safety most studies report AEs for ATD without distinction between PTU, TMZ or carbamizole. For TMZ alone rates are between 15.5% and 30%, including: pruritus and hives, skin rash; diffuse arthralgia, muscle pain, and/or joint pain; vasculitis; haematological events including lymphopenia, eosinophilia, neutropenia; Stevens-Johnson syndrome; mild liver injury. AEs affecting the liver are typically associated with the use of ATD, although analysis of the ARES database of the FDA for severe liver injury adverse events over all age groups revealed a markedly higher frequency with propylthiouracil than with thiamazole. Occurrence of AEs appears to be dose-dependent.

- **Overall conclusion**

The benefit/risk profile for the use of TMZ in paediatric patients is acceptable and comparable to the adult population. Insufficient data exist for the use of TMZ in children younger than 2 year of age. Please refer to the recommendation.

- **Recommendation**

SPC section 4.2
The proposed new wording from Sanofi-Aventis Deutschland GmbH in the SPC for Thiamazol is accepted.
In the SPC for Thyrozol from Merck the following should be added: "*Safety and efficacy of thiamazole in children below 2 year of ages have not been evaluated systematically. Use of thiamazole in children below two years of age is therefore not recommended."*

SPC section 4.5
The sentence: *"Interaction studies have not been performed in paediatric patients"* should be added in both SPCs.

SPC section 4.8
The proposal by Sanofi-Aventis Deutschland GmbH:
Paediatric population
Frequency, type and severity of adverse reactions in children appear to be comparable with those in adults. Severe cutaneous hypersensitivity reactions reported in both adult and paediatric patients, namely Stevens-Johnsons syndrome, are already implicitely labeled ("Very rare including isolated reports: Severe forms, including generalised dermatitis, have only been described in isolated cases.") is endorsed and should be added in both SPCs.

SPC section 5.2
The proposal of the inclusion of the results of one paediatric PK study is not considered of relevance.

There are no further changes needed to the SPCs.

VI. ASSESSMENT OF RESPONSE TO QUESTIONS IN PRELIMINARY PAEDIATRIC AR / MS D85 COMMENTS

SmPC Section 4.2

Rapporteur
Based upon the Critical Expert Reports on the paediatric data submitted by Sanofi-Aventis and Merck, the Rapporteur's overall conclusion and recommendations were:
"The benefit/risk profile for the use of TMZ in paediatric patients is acceptable and comparable to the adult population. Insufficient data exist for the use of TMZ in children younger than 2 year of age. Please refer to the recommendation"
SmPC Section 4.2:
"The proposed new wording from Sanofi-Aventis Deutschland GmbH in the SPC for Thiamazol is accepted. In the SPC for Thyrozol from Merck the following should be added: "Safety and efficacy of thiamazole in children below 2 year of ages have not been evaluated systematically. Use of thiamazole in children below two years of age is therefore not recommended

COMPANYS RESPONSES

Sanofi-Aventis
No action required.
The Rapporteur's recommendation for PI amendments (SmPC Section 4.2) has been already part of the proposed PI amendments by Sanofi-Aventis.
However, SmPC section 4.2 has been amended to address the recommendation made by AFSSAPS (see below).

Merck
The MAH has amended the new wording in the SmPC 4.2)

Rapporteur's comment
Accepted

FR comments:
The French regulatory agency proposes the following modifications with regard to the proposed PI amendment, which is related to SmPC Section 4.2
"However we would like to propose the following modification for section 4.2.
Indeed, there is a discrepancy between the first paragraph (3 to 17 years of age) and the second paragraph (under 2 years of age). It should be clarified that safety and efficacy of thiamazole have not been evaluated systematically in children of 2 years of age.

Paediatric population
Use in children and adolescents (3 to 17 years of age)
Initial dosage for the treatment of children and adolescents above 3 years of age should be adjusted to the body weight of the patients. Usually treatment is initiated at a daily dose of 0.5 mg/kg, divided into two or three equal doses. For maintenance therapy, the daily dose can be reduced depending on the response of the patient to the treatment.
Use in children (under 2 year**s** of age **and under**)

Safety and efficacy of thiamazole in children below 2 year of ages have not been evaluated systematically. Use of thiamazole in children below two years of age is therefore not recommended"

SE comments

In general, the MPA agrees to the overall position and recommendations of the Rapporteur in terms of TMZ product labelling, but additional points that are related to paediatric dosing are raised

"Only one thiamazole product (Thacapzol, 5 mg) is currently available in Sweden. This nationally approved product does not include any paediatric posology. Since the posology has already been approved for the products by the MAHs participating in this pdWS procedure, no assessment of the posology is included in this report.."

Based on the above, the MPA requests supplementary information to justify the paediatric posology in the PI already approved and to support the proposed paediatric posology in the amended TMZ PI.

SmPC Section 4.2:

Request for Supplemental Information on Approved Paediatric Posology:

"Inclusion of a paediatric posology would be desirable; however, in order to accept the posology the MPA would need information on the data that support the wording already approved for these products. It is therefore kindly requested that an overview of data supporting the posology is submitted by the MAH.

Request for Supplemental Information on and Recommendations for Proposed Paediatric Posology:

"Furthermore, if implementation of the proposed wording should be meaningful when the posology is not approved (as is the case in Sweden), the posology wording should also be included in the text proposed within this procedure.

Therefore, provided that supportive data is made available, the MPA propose that the entire paediatric wording in section 4.2 is included in the recommended text to be implemented:

Paediatric population

Use in children and adolescents (3 to 17 years of age)

Initial dosage for the treatment of children and adolescents above 3 years of age should be adjusted to the body weight of the patients. Usually treatment is initiated at a daily dose of 0.5 mg/kg, divided into two or three equal doses. For maintenance therapy, the daily dose can be reduced depending on the response of the patient to the treatment.

Use in children (under 2 year of age)

Safety and efficacy of thiamazole in children below 2 year of ages have not been evaluated systematically. Use of thiamazole in children below two years of age is therefore not recommended.

It should further be considered to amend the posology with a maximal recommended dose since the highest recommended adult dose of 40 mg otherwise will be exceeded in children/adolescents with a body weight above 80 kg"

COMPANY RESPONSE

Sanofi-Aventis

Prior to the SmPC amendments proposed by Sanofi-Aventis in the frame of the Art 45 Worksharing Procedure, there has been no approved paediatric dosing recommendations in the PI on Thiamazol Henning®.
Therefore, Sanofi-Aventis is deemed not to be in a position to provide data in support of an already approved paediatric posology in the PI.

Ad 2):

Summary of Data on Recommended Dosing in the Paediatric Population

The amendments of SmPC Section 4.2 as proposed by Sanofi-Aventis in the frame of the Art 45 Worksharing Procedure (inclusion of paediatric dosing recommendations) are based upon the identified clinical studies in the paediatric population assessed in the Critical Expert Report submitted by Sanofi-Aventis. In order to address MPA's request, Sanofi-Aventis has additionally conducted an add-on literature search to identify further scientific publications related to paediatric TMZ dosing. Apart from data already submitted with the Critical Expert Report that triggered the proposed amendment of SmPC Section 4.2 (inclusion of paediatric dosing recommendations into the PI), only one additional publication, a Japanese retrospective study, has been retrieved:
Matsushita et al. – Initial treatment of pediatric Graves' disease with methimazole: a retrospective follow-up study (Clin Pediatr Endocrinol 2010;19(4)).
This publication as well as a brief summary of sections of the Critical Expert Report related to paediatric TMZ dosing are provided:

Retrospective Follow-up Study on Paediatric Dosing

According to a questionnaire survey in Japan, more than half of the paediatric endocrinologists started with a TMZ dose of 1 mg/kg/day, in many cases exceeding the dose recommendations for adults.
This retrospective follow-up study compared high and low doses of TMZ in children newly diagnosed with Graves' disease (Matsushita et al. 2010). Although the initial TMZ dose for paediatric Graves' disease is usually 0.5-1.0 mg/kg/day, given either QD or BID, the most appropriate starting dose is not clearly defined. Therefore, the efficacy of different TMZ doses was compared in a total of 27 Japanese children

- A TMZ high-dose group (≥ 0.7 [mean 0.85 ± 0.13] mg/kg/day; n=8; age range: 3.2 to 13.7 years);
- A TMZ low-dose group (< 0.7 [mean 0.51 ± 0.12] mg/kg/day; n=19; age range: 4.3 to 16.8 years).

There were no significant differences between free T4 or thyroid-stimulating hormone receptor antibody levels between the groups before treatment. There was no significant difference in the mean time required to normalise free T4 levels between the high- and low-dose groups. In addition, no other factor influenced the time to efficacy of TMZ. A TMZ dose of < 7 (0.51 ± 0.12) mg/kg/day appears to be as effective as a higher dose in normalising the serum free T4 level in children with mild to moderate Graves' disease. There were also a few patients with severe disease included, with no clear differentiation in effect between TMZ high- and low-doses. This suggests that even in severe disease, low-dose TMZ might be appropriate, but due to the low number of subjects included, not definite conclusion can be drawn.

Summary of Critical Expert Overview on Paediatric Dosing

The paediatric dose recommendations proposed by Sanofi-Aventis for updating the PI as triggered by the Critical Expert Report on the retrieved paediatric data has been based on the following:

The adequate initial dosing had been a matter of debate for a long time. Some investigators used a fixed starting dose between 10 mg and 40 mg TMZ daily (Barrio et al. 2005, Reinwein et al. 1993), while others calculated the initial dose based on the body weight or the body surface of the individual patient. In these studies, initial dosing ranged between 0.3 and 2 mg/kg daily (Mussa et al. 1999, Sato et al. 2007). Most of the studies used initial daily doses around 0.5 mg/kg, administered three times daily (TID) or twice daily (BID) (Dötsch et al. 2003).

The occurrence of adverse events appears to be dose-dependent. Reinwein et al. (1993) compared a low dose of TMZ (10 mg/day) and a high dose (40 mg/day) in paediatric patients. The rate of adverse drug reactions was 15.5% in the 10 mg/day group and 26.5% in the 40 mg/day group (significant difference). Main adverse events were pruritus, rash, and haematologic events.

Based on the available clinical data in the paediatric population, the following dosing recommendations for TMZ in the paediatric population has been made (refer to Critical Expert Report previously submitted;
Initial dosage for the treatment of children and adolescents above 3 years of age should be adjusted to the body weight of the patients. Usually treatment is initiated at a daily dose of 0.5 mg/kg, divided into two or three equal doses. For maintenance therapy, the daily dose can be reduced depending on the response of the patient to the treatment.

Safety and efficacy of TMZ in children below 2 year of ages have not been evaluated systematically. Use of TMZ in children below two years of age is therefore not recommended.

Although considerable heterogeneity exists with the respect to the TMZ starting dose used in paediatric patients, a daily dose of about 0.5 mg/kg is deemed advisable by most researchers.

Lower doses tend to delay the time until the euthyroid state is reached, while adverse events related to TMZ appear to be dose-dependent.

Only two of the identified and reviewed paediatric studies explicitly included patients of or below 2 years of age (Collen et al. 1980: age range of 7 months to 19 years; Dötsch et al. 2000: age range of 1.1 years to 17 years), while typically TMZ treatment is initiated in older children.

Although no evidence was found for special precautions necessary for children below 2 years of age, it is considered appropriate to refrain from recommending TMZ in children below 2 years of age base on the paucity of the available data.

In conclusion, the paediatric TMZ dosing recommendations proposed by Sanofi-Aventis appear to be sufficiently supported by the available clinical evidence (refer to Critical Expert Report), including the additionally identified retrospective study by Matsushita et al. (2010).

Maximum Recommended Dose in the Paediatric Population
With regard to the maximum recommended dose as suggested by MPA, there are unfortunately no data on patients' body weight given in those publications dealing with paediatric TMZ dosing solely on a mg/kg daily dose. Therefore, it cannot be derived whether some of the paediatric patients studied received absolute daily TMZ doses above those recommended for adults.
Based on the currently proposed recommended TMZ starting dose of 0.5 mg/kg/day, paediatric patient subsets above 80 kg body weight would be dosed with an absolute daily dose exceeding the one proposed for adults (40 mg TMZ daily).
Therefore, and in line with suggestions from MPA, Sanofi-Aventis proposes to include the following addition to the respective PI wording:

Paediatric population
Use in children and adolescents (3 to 17 years of age)
...
A total daily dose of 40 mg thiamazole should not be exceeded.
...
This recommendation is deemed to be well in line with Reinwein et al. (1993; high-dose group receiving 40 mg TMZ, see Table 1), with Collen et al. (1980; patients > 38 kg receiving 30 mg daily, see Table 1), and also with Bossowski et al. (2005) reporting a maximum TMZ dose of 30 mg/m2.

Proposed Final Product Information Wording
Based on the suggestions made above in response to recommendations made by AFSSAPS and MPA and in compliance with the Rapporteur's position, the final PI wording proposed by Sanofi-Aventis is as follows:

Paediatric population
Use in children and adolescents (3 to 17 years of age)
Initial dosage for the treatment of children and adolescents above 3 years of age should be adjusted to the body weight of the patients. Usually treatment is initiated at a daily dose of 0.5 mg/kg, divided into two or three equal doses. For maintenance therapy, the daily dose can be reduced depending on the response of the patient to the treatment.
A total daily dose of 40 mg thiamazole should not be exceeded.

Use in children (2 years of age and under)
Safety and efficacy of thiamazole in children below 2 year of ages have not been evaluated systematically. Use of thiamazole in children below two years of age is therefore not recommended.

Merck
If hyperthyroidism in children is not recognised and treated, it can seriously interfere with growth and development (*see Segni et al. 1999*). Antithyroid drugs are often the preferred therapeutic option and the recommendations for treatment described generally apply also to children (*see Grüters 1998*). Main indications for the use of thiamazole in children were Graves' disease and unspecified hyperthyroidism. In these indications, thiamazole was effective in reaching euthyroidism and/or a disease remission.

Indications and dosages of thiamazole in children are already listed in the product information.

Concerning Thyrozol (thiamazole, methimazole), no clinical trials in children were carried out by Merck KGaA. Table 1 provides an overview on the publications the pharmacokinetic of thiamazole has been investigated in children and adolescents with Graves' disease (n = 9). Large interindividual differences were noted but the parameters were relatively reproducible in the same subject. Plasma levels of thiamazole showed peak concentrations of 4.4 to 12.6 µmol/l at 0.5 to 4 h after drug administration (175 µmol/m2).

Plasma half-life and area under the curve ranged from 2.73 to 6.04 h, 32.8 to 77.9 µmol/l/h, respectively. There was a good correlation between intrathyroidal concentrations and daily dose per unit of body surface, but not with the mode of drug administration and with the interval between the last dose and surgery (*see Okuno, 1987*).

The daily doses of thiamazole used to treat hyperthyroidism in children and adolescents range considerably according to the severity of the disease. However, a mean initial dose of 0.5 mg/kg once daily is generally considered in this population (*see Dötsch, 2000*; *Dötsch, 2003*; *Grüters-*

Kieslich et al., 2003). After normalisation of the thyroid function the dose is stepwise reduced to a lower maintenance dose which depends on the metabolic condition of the patient. Additional treatment with levothyroxine may be required to avoid hypothyroidism and to enable less frequent monitoring (*see Grüters, 1998*).

The following wording is reflecting the mentioned data *Paediatric population*
Use in children and adolescents (3 to 17 years of age)
Initial dosage for the treatment of children and adolescents (3 to 17 years of age) is dependent on the body weight of the patients. Usually, treatment is initiated at a daily dose of 0.5 mg/kg, divided into two or three equal doses. The maximal recommended dose is 40 mg/day, regarding children or adolescents with more than 80 kg bodyweight. For maintenance therapy, the daily dose can be reduced and given once daily, depending on the response of the patient to the treatment. Additional treatment with levothyroxine may be required to avoid hypothyroidism.

Use in children (2 years of age and under)
Safety and efficacy of thiamazole in children 2 year of ages and under have not been evaluated systematically. Use of thiamazole in children 2 year of ages and under is therefore not recommended.

Rapporteur's comment
As recommended by the MPA both companies has amended the posology with a maximal recommended dose of 40 mg that otherwise will be exceeded in children/adolescents with a body. The wording suggested by Sanofi-Aventis seems most adequate and this is accepted.

SmPC Section 4.5

Rapporteur
The sentence: *"Interaction studies have not been performed in paediatric patients"* should be added in both SPCs.

COMPANY RESPONSE

Sanofi- Avenetis
No action required. The Rapporteur's recommendation for PI amendments (SmPC Section 4.5) has been already part of the proposed PI amendments by Sanofi-Aventis

Merck
The MAH agrees with the proposed wording.

Rapporteur's comment
Accepted

SmPC Section 4.8

Rapporteur
The proposal by Sanofi-Aventis Deutschland GmbH: Paediatric population - Frequency, type and severity of adverse reactions in children appear to be comparable with those in adults. Severe cutaneous hypersensitivity reactions reported in both adult and paediatric patients, namely Stevens-Johnsons syndrome, are already implicitely labeled ("Very rare including

isolated reports: Severe forms, including generalised dermatitis, have only been described in isolated cases.") is endorsed and should be added in both SPCs.

COMPANY RESPONSE

Sanofi-Aventis
No action required. The Rapporteur's recommendation for the PI (SmPC Section 4.8) has been already part of the proposed PI amendments by Sanofi-Aventis. However, a slight amendment in the PI wording is proposed by Sanofi-Aventis in order to separate the actual labelling from the justification to include 'Stevens-Johnson syndrome' explicitly in the PI, although one can argue that it has been already implicitly labelled in the former PI texts: *"Very rare including isolated reports: Severe forms, including generalised dermatitis, have only been described in isolated cases."*

Therefore, the following final wording is proposed, which leaves the content, i.e. explicit inclusion of Stevens-Johnson syndrome into the labelling, unaltered:

Paediatric population
Frequency, type and severity of adverse reactions in children appear to be comparable with those in adults. Severe cutaneous hypersensitivity reactions have been reported in both adult and paediatric patients, including Stevens-Johnson syndrome (very rare including isolated reports: severe forms, including generalised dermatitis, have only been described in isolated cases).

Merck
With regards to the frequency, type and severity of adverse reactions, please see statement for paediatric population.
The risk of severe forms of allergic skin reaction, including generalized dermatitis is listed in the Reference Safety Information (RSI), i.e. Company Core Safety Data Sheet (CSDS) dated 04 March 2011, for thiamazole, as well as in the Summary of Product Characteristics of Thyrozol®/thiamazole. However, Stevens Johnson Syndrome (SJS)/Toxic Epidermal Necrosis (TEN) are not listed in these documents, being both more severe (i.e., potentially lifethreatening) and more specific (severe acute epidermolytic dermopathies) than the listed terms.

An in-depth review of the Company data and of the literature to assess the risk of Stevens-Johnson syndrome and Toxic Epidermal Necrosis in associated with thiamazole has been performed by the Company (see the Pharmacovigilance Expert Statement on Thiamazole and SJS/TEN). Based on this review, the Company is of the opinion that the threshold of evidence for a reasonable possibility of a causal relationship between thiamazole and SJS/TEN has not been reached. However, because both events are usually drug-related, medically significant and potentially life-threatening, the Company considers them as signals, to be followed with the inclusion of SJS/TEN in the Areas for Close Monitoring.

Rapporteur's comment
The final wording propose by Sanofi-Aventis is endorsed as it seems relevant explicit to include the information of Stevens-Johnson syndrome. The wording should also be included in the SmPC by Merck.

SmPC Section 5.2

Rapporteur
The proposal of the inclusion of the results of one paediatric PK study is not considered of relevance.

COMPANY RESPONSE

Sanofi-Aventis
The Rapporteur's recommendation to omit the paragraph in the proposed PI (SmPC Section 5.2) is accepted.

Merck
The company do not discuss the recommendation although they are referring to one small paediatric PK study and include the data in their SmPC.

Rapporteur's comment
The inclusion of the results of one single paediatric PK study is still not considered of relevance

VII. ASSESSMENT OF RESPONSE TO FINAL PAEDIATRIC AR

SmPC section 4.2

Response from Merck:
Thiamazole is indicated in adults as well as in children, e.g. for the treatment of hyperthyroidism due to Graves'disease, as well as in the preparation for surgery in all forms of hyperthyroidism. In these indications full suppression of the thyroid gland is required. Tamai et al. (1995) demonstrated in a study with adult patients with Graves' disease a positive influence of a combined antithyroid drug treatment (ATD) and levothyroxine (T4) treatment and continuation of T4 administration after ATD on long-term remission. To avoid hypothyroidism substitution of T4 is recommended especially in paediatric patients. "In children, a combination of ATD and T4 is routine, since it prevents the development of hypothyroidism and enables less frequent monitoring." (Grüters et al. 1998).
Therefore the MAH would like to maintain the proposed statement in the first paragraph:
Additional treatment with levothyroxine may be required to avoid hypothyroidism.

Rapporteur' comment
The statement by the MAH is of clinical relevance and the wording is accepted

SmPC section 4.8

Response from Merck:
The PSUR Worksharing (WS) procedure for thiamazole (PL/H/PSUR/0021/001) was finalized on 26 June 2011 by the P-RMS (Polish health authority). The assessor concluded in the Final Assessment Report that there is currently no sufficient evidence to include Stevens-Johnson Syndrome (SJS) as an adverse reaction into the SmPC. The MAH is asked to further closely monitor the ADR SJS and present cumulative analysis of SJS cases in the next PSUR (see Appendix 1). The MAH would like to point out that the discussion in the PSUR WS took into

account the literature (e.g. Rivkees SA et al., 2010) also submitted to the Paediatric WS procedure.

Within this Paediatric WS procedure the MAH submitted a detailed assessment of the risk of SJS and Toxic Epidermal Necrolysis (TEN) in association with the use of thiamazole (see Appendix 2). Based on currently available literature and in house-data the MAH concluded that the threshold of evidence for a reasonable possibility of a causal relationship between thiamazole and SJS/TEN has not been reached.

In conclusion, the MAH does not see a reason for a divergent decision on an issue, which was recently decided in the parallel procedure of the PSUR WS. Therefore, the MAH believes that the inclusion of SJS in the SmPC for thiamazole is not warranted at this point in time. However, since SJS is usually drug-related, medically significant and potentially life-threatening, the MAH considers it as signal, to be followed with the inclusion of SJS in the areas for close monitoring

Rapporteur's comment
Despite the conclusion of the PSUR Worksharing (WS) procedure for thiamazole (PL/H/PSUR/0021/001), the danish assessor is still of the opinion that SJS should be included in the SPC. There has been isolated cases of SJS where a relationship to thiamazole could not be excluded and SJS is most often drug induced.

VIII. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

The benefit/risk profile for the use of TMZ in paediatric patients is acceptable and comparable to the adult population. Insufficient data exist for the use of TMZ in children younger than 2 year of age. Please refer to the recommendation.

➢ Recommendation

Based on the review of the presented paediatric data it is recommended that all thiamazole containing products across the EU should include the following wordings in the SmPC:

SmPC section 4.2

Paediatric population
Use in children and adolescents (3 to 17 years of age)
Initial dosage for the treatment of children and adolescents above 3 years of age should be adjusted to the body weight of the patients. Usually treatment is initiated at a daily dose of 0.5 mg/kg, divided into two or three equal doses. For maintenance therapy, the daily dose can be reduced depending on the response of the patient to the treatment. Additional treatment with levothyroxine may be required to avoid hypothyroidism.
A total daily dose of 40 mg thiamazole should not be exceeded.

Use in children (2 years of age and under)
Safety and efficacy of thiamazole in children below 2 year of ages have not been evaluated systematically. Use of thiamazole in children below two years of age is therefore not recommended.

SmPC section 4.5
"Interaction studies have not been performed in paediatric patients"

SmPC section 4.8

Paediatric population
Frequency, type and severity of adverse reactions in children appear to be comparable with those in adults. Severe cutaneous hypersensitivity reactions have been reported in both adult and paediatric patients, including Stevens-Johnson syndrome (very rare including isolated reports: severe forms, including generalised dermatitis, have only been described in isolated cases).

Type IB variation (C.I.3 a) to update sections 4.2, 4.5 and 4.8 of the SmPC and the appropriate sections of the PL to be requested from the MAH by 24 October 2011.

IX. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable

X. AUTHORISATION HOLDERS INVOLVED

MAH	MS	Name of the medicinal product	Strenght	Pharmaceutical form
SANOFI-AVENTIS DEUTSCHLAND GMBH	DE	THIAMAZOL 40 MG INJECT. HENNING	40 mg	solution for injection
SANOFI-AVENTIS DEUTSCHLAND GMBH	DE	THIAMAZOL 5 MG HENNING	5 mg	film-coated tablet
Merck KGaA	BG	Thyrozol 5	5 mg	tabl.
Merck KGaA	CZ	Thyrozol 5	5 mg	tbl obd
Merck Pharma GmbH	DE	Thyrozol 10 mg	10 mg	film-coated tablet
Merck Pharma GmbH	DE	Thyrozol 20 mg	20 mg	film-coated tablet
Merck Pharma GmbH	DE	Thyrozol 5 mg	5 mg	film-coated tablet
Merck KGaA	LV	Thyrozol 10 mg apvalkotās tabletes	10 mg	Film-coated tablets
Merck KGaA	LV	Thyrozol 5 mg apvalkotās tabletes	5 mg	Film-coated tablets
Merck KGaA	LT	Thyrozol 5 mg, plėvele dengtos tabletės	5 mg	Film-coated tablets
Merck KGaA	LU	Thyrozol 10 mg	10 mg	film-coated tablet
Merck KGaA	LU	Thyrozol 20 mg	20 mg	film-coated tablet
Merck KGaA	LU	Thyrozol 5 mg	5 mg	film-coated tablet
Merck Pharma GmbH	RO	Thyrozol 10 mg	10 mg	film-coated tablet
Merck Pharma GmbH	RO	Thyrozol 20 mg	20 mg	film-coated tablet

Merck Pharma GmbH	RO	Thyrozol 5 mg	5 mg	film-coated tablet
Merck KGaA	LU	Thyrozol 10 mg	10 mg	film-coated tablet