

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

**Levothyroxine
(L-thyroxine)**

SE/W/004/pdWS/001

Rapporteur:	Sweden
Start of the procedure (day 0):	27 March 2009
Finalisation procedure (day 120):	10 December 2009
Date of this report	23 April 2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VIII
INN (or common name) of the active substance(s):	L-thyroxine
MAH (s):	sanofi aventis (see section VIII)
Pharmaco-therapeutic group (ATC Code):	H03AA01
Pharmaceutical form(s) and strength(s):	- tablets 25, 50, 75, 100, 125, 150, 175, 200 µg and 1 mg - solution for injection 500 µg - drops 100 µg/ml

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I. EXECUTIVE SUMMARY

Levothyroxine belongs to the pharmacological group of thyroid hormones. The effect of synthetic levothyroxine is identical with that of the principal hormone of the thyroid gland.

Levothyroxine is mainly indicated in the treatment of hypothyroidism as a substitution therapy. Most levothyroxine products have been nationally approved, and in most cases the posology includes dosage recommendations for paediatric patients, in line with the recommendations given in current guidelines concerning the treatment of congenital hypothyroidism.

In the clinical overview provided by the MAH (sanofi-aventis), publications on the choice of dose in patients with congenital hypothyroidism (CH) and with the possible use of levothyroxine in other indications (preterm infants, Down syndrome and autoimmune disease (T1D)) are presented and discussed. No new data to be included in the SPC has been provided.

The assessment of the use of levothyroxine in paediatric patients has, however, shown that the wording of the posology section varies a lot in different countries and also between different levothyroxine products. It is therefore suggested that the paediatric posology is harmonised in a type II variation.

II. RECOMMENDATION

The new data presented by the MAH does not call for any amendment of new information in the product information of levothyroxine.

It is suggested that the paediatric posology is harmonised in a type II variation within 60 days after finalising this procedure. The following wording in section 4.2 regarding the use of levothyroxine in congenital and acquired hypothyroidism in paediatric patients is suggested:

Paediatric patients

The maintenance dose is generally 100 to 150 micrograms per m² body surface area.

For neonates and infants with congenital hypothyroidism, where rapid replacement is important, the initial recommended dosage is 10 to 15 micrograms per kg BW per day for the first 3 months. Thereafter, the dose should be adjusted individually according to the clinical findings and thyroid hormone and TSH values.

For children with acquired hypothyroidism, the initial recommended dosage is 12.5-50 micrograms per day. The dose should be increased gradually every 2 to 4 according to the clinical findings and thyroid hormone and TSH values until the full replacement dose is reached.

Infants should be given the total daily dose at least half an hour before the first meal of the day.

When applicable:

Tablets are to be disintegrated in some water (10 to 15 mL) and the resultant suspension, which must be prepared freshly as required, is to be administered with some more liquid (5 to 10 mL).

Where necessary the package leaflet should be changed accordingly.

III. INTRODUCTION

In accordance with Article 45 of the Regulation (EC) No. 1901/2006, the CMD(h) and the EMEA require that for authorized medicinal products, paediatric studies not previously submitted should be submitted for assessment to European Health Agencies.

Only one MAH (sanofi aventis) has prepared a clinical overview (CO) in the context of this work-sharing procedure for paediatric studies for levothyroxine. The aim of this CO is to clarify the context of the data already listed by sanofi aventis affiliates as well as their relevance for EU situation. The CO is based on published literature data and internal sanofi-aventis safety data from post-marketing experiences.

An updated line listing on reported adverse events in patients below the age of 18 from launch to 21st Jan 2009 has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for levothyroxine and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing
- The SPC wording of section 4.1 and 4.2 related to the paediatric use of the medicinal product (see section IV).

IV. SCIENTIFIC DISCUSSION

L-thyroxine (levothyroxine) belongs to the pharmacological group of thyroid hormones (ATC code: H03AA01). The effect of synthetic levothyroxine is identical with that of the principal hormone of the thyroid gland, thyroxine (T₄), which is produced in the thyroid from iodine and tyrosine.

Levothyroxine is mainly indicated in the treatment of hypothyroidism.

The **approved indications in paediatric population** are the following:

- In Germany, levothyroxine tablets, solution for injection and drops are indicated as a replacement therapy in hypothyroidism, the drops especially in neonates and infants.
- In Spain, it is indicated as replacement therapy when thyroid function is either depressed or absent, as in hypothyroidism in general including hypothyroid states in children.
- In other EU countries (Austria, Hungary, Portugal) there is no specific paediatric indication labelled as such. However, some dosage recommendations are given.

The current paediatric data assessment concerns data submitted by sanofi-aventis only. The first marketing authorisation (MA) for levothyroxine from sanofi-aventis was received in 1967, and levothyroxine is currently registered and marketed by sanofi-aventis and its affiliates in 5 countries in Europe (Austria, Germany, Hungary, Portugal, Spain).

The submitted paediatric data was discussed in a Clinical Overview.

Current paediatric dosage recommendations for sanofi-aventis products

There is no harmonised SPC for levothyroxine products marketed by sanofi-aventis in Europe. The MAH refers to the Company Core Data Sheet for safety information.

Different countries have somewhat different recommendations for paediatric use of levothyroxine. The sanofi-aventis products have the following recommendations:

In Germany (drops), the initial recommended dosage is 10 to 15 micrograms per kg BW per day for the first 3 months for infants with congenital hypothyroidism. Thereafter, the dose should be adjusted individually according to the clinical findings and thyroid hormone and TSH values. For children with hypothyroidism, the initial recommended dosage is 8 to 10 micrograms per kg BW per day. The maintenance dose should be 100 to 150 micrograms per m² body surface area. The dose must always be adjusted to the individual needs. Infants should be given the total daily dose at least half an hour before the first meal of the day.

In Germany (tablets, solution for injection) and Austria (tablets), the initial recommended dosage for children is 12.5-50 micrograms per day, for newborns 25-50 micrograms per day. The replacement dose during long-term therapy should depend, amongst other things, on the age and body weight of the individual child:

Age	Dose µg/day	Dose µg/kg/day
0-6 months	25-50	10-15
6-24 months	50-75	8-10
2-10 years	75-125	4-6
10-16 years	100-200	3-4
> 16 years	100-200	2-3

In case of congenital hypothyroidism, same recommendations are given as for drops. For tablets, an additional recommendation is given to allow the tablets to disintegrate in a little water, and give the resulting fine suspension with a little more liquid (prepare freshly each time).

In Hungary, there is no dosage recommendation. However, it is mentioned that for children the tablet should be dissolved in a small amount of water, and then further diluted with fluid.

In Portugal and Spain, the recommended dosage in growing children is up to 400 micrograms per day. The euthyroid state has to be achieved as soon as possible due to the possible growth and tissues maturation retardation linked to the thyroid hormone insufficiency.

Current paediatric dosage recommendations for other levothyroxine products

Levothyroxine is also available in Europe in products registered and marketed by other MAHs, e.g. Nycomed (Levaxin) and Merck Germany (Euthyrox).

Euthyrox, marketed by Merck in several EU countries via MRP DE/H/284, has the following recommendations for paediatric patients:

The individual daily dose should be determined on the basis of laboratory tests and clinical examinations. As a number of patients show elevated concentrations of T₄ and fT₄, basal serum concentration of thyroid-stimulating hormone provides a more reliable basis for following treatment course. Except for neonates, where rapid replacement is important, thyroid hormone therapy should be started at low dose and increased gradually every 2 to 4 weeks until the full replacement dose is reached.

Indication	Recommended dose (microgram levothyroxine sodium/day)
<i>Substitution therapy in hypothyroidism in children</i>	
- initial dose	12.5 - 50
- maintenance dose	100 - 150 microgram/m ² body surface

The daily doses can be given in a single administration.

Ingestion: as a single daily dose in the morning on an empty stomach, half an hour before breakfast, preferably with a little liquid, (for example, half a glass of water).

Infants receive the entire dose at once at least 30 minutes before the first meal of the day. Tablets are to be disintegrated in some water and the resultant suspension, which must be prepared freshly as required, is to be administered with some more liquid.

Assessor's comment:

Levothyroxine has been in use for more than 50 years in the treatment of hypothyroidism in both paediatric and adult patients. Since substitution with levothyroxine in congenital hypothyroidism is vital to normal development and in some cases to survival, recommendations on how to treat paediatric patients is included in most SPCs. As seen above, although differently worded, the recommendations are similar with regards to congenital hypothyroidism whereas the recommendations for treating acquired hypothyroidism differ slightly, especially regarding initial dose (8-10 µg/kg/d vs 12.5-50 µg/d).

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

Levothyroxine from sanofi-aventis is available as the following pharmaceutical formulations:

- Levothyroxine tablets 25, 50, 75, 100, 125, 150, 175, 200 µg and 1 mg
- Levothyroxine solution for injection 500 µg
- Levothyroxine drops 100 µg/ml

Assessor's comment:

Levothyroxine solution for injection and drops are not approved in all MS. Levothyroxine tablets are available in a wide range of strengths, which makes it possible to dose per kg also when using tablets.

IV.2 Non-clinical aspects

No non-clinical studies on juvenile animals were performed by sanofi-aventis or have been identified in the published literature.

IV.3 Clinical aspects

1. Introduction

The submission includes Module 1, Module 2 and Module 5. Module 5 contains a line listing of post-marketing experience in paediatric patients and 23 literature references (including an in-house CO on levothyroxine oral drops). Another 4 literature references are cited in the CO but were not submitted.

Congenital hypothyroidism

Congenital hypothyroidism (CH) affects approximately one in 3000 to 4000 infants. It has long been known that mental development in children with congenital hypothyroidism is related to adequacy of treatment. Beginning treatment before three months of age improves the prognosis for mental

development in these children (13). Therefore, newborn screening programs have been initiated such as the program described by Grant in 1995 (1).

Guidelines for neonatal screening programmes for congenital hypothyroidism have been published in 1993 by the European Society for Paediatric Endocrinology (2). Regarding the initial treatment, these guidelines state that levothyroxine is the medication of choice and should be immediately instituted in all cases with markedly elevated Thyroid Stimulating Hormone (TSH), with a dose of 10-15 µg/kg. A monitoring of treatment should be done using hormonal measurements. These treatment recommendations were not changed in an update review published in 2007 (4).

Acquired hypothyroidism

Acquired hypothyroidism in children include autoimmune thyroiditis, drug-induced hypothyroidism, endemic goiter due to nutritional iodide deficiency, irradiation of the thyroid and surgical excision of the thyroid. Once the diagnosis of hypothyroidism is confirmed, levothyroxine therapy should be started with an initial dosage of 0.05 mg per day (13). One author (7) proposed levothyroxine dosages in children with hypothyroidism resulting from thyroiditis, which decrease on a weight basis with age:

Age	Na-L-Thyroxine (µg/kg)
0-3 months	10-15
3-6 months	8-10
6-12 months	6-8
1-3 years	4-6
3-10 years	3-4
10-15 years	2-4
> 15 years	2-3

Assessor's comment:

Congenital hypothyroidism (CH) was first described in the late 19th century and different preparations of thyroid hormones have long been used to treat hypothyroidism. Levothyroxine has been in use for more than 50 years in the treatment of hypothyroidism in both paediatric and adult patients. There are a number of different levothyroxine products, most being nationally approved. Thus, the knowledge on how to use levothyroxine is mainly based on vast clinical experience and to some extent on retrospective studies or non controlled trials. The dose recommendations for the treatment of CH are supported by clinical trials (Fisher & Foley, Pediatrics 1989; Germak & Foley, J Pediatr 1990). The same recommendations are given by the European Society for Paediatric Endocrinology (2, 4) and the American Academy of Pediatrics (Pediatrics, 2006; 117:2290-2303). The importance of fast normalisation of thyroid status in CH to ensure normal neurodevelopment is well known, although there is still insufficient knowledge on the optimal dose regimen especially with regards to the long-term effects on growth and development.

The issue of acquired hypothyroidism is not discussed in the provided overview. In these cases rapid normalisation is not as important as in CH.

2. Clinical studies

The critical expert overview is a review of published literature between 1992 and 2009.

Assessor's comment:

The overview mainly deals with issues on the choice of dose in patients with congenital hypothyroidism (CH) and with the possible use of levothyroxine in other indications (preterm infants, Down syndrome and autoimmune disease (Type 1 diabetes [T1D])).

➤ **Efficacy**

Congenital hypothyroidism:

- Grüters 1999 (3)

This report on the clinical experience with levothyroxine oral drops was submitted by sanofi aventis affiliates (3).

In this document, the expert made a review of the clinical pharmacology and of the clinical efficacy data of the drug. Regarding efficacy, after a literature review, the expert reported the first experiences of the Department of Paediatrics at the Charité Hospital in Berlin, Germany, with this formulation:

“Our own initial results with the use of L-thyroxine sodium in liquid solution in five neonates with congenital hypothyroidism in a concentration of 5 µg/drop showed that normalisation of TSH levels in a total dose of 35 µg/day appears somewhat slower compared to the tablet dosage form with a dose of 50 µg/day. Therefore the currently recommended initial dose should be 40 µg/day corresponding to 8 drops/day. “

According to expert’s conclusions, studies have shown that there are no relevant differences in absorption between the tablet and liquid dosage forms. This, coupled with the fact on administration of the liquid form, levels in neonates and infants were stable after 14 days and the TSH had already normalised in half the patients after 14 days, means that there are no reservations against the use of the liquid dosage form in neonates and infants, since no disproportionately long period of hypothyroidism is likely after the start of replacement therapy. The risk of overdosage appears significantly reduced with use of the L-thyroxine oral drops and the aim of treatment – a normal childhood development – is achieved with relatively lower doses. These experiences raise no concerns about the use of liquid dosage forms in older children and adults with hypothyroidism in whom, for example, the administration of tablets is not possible. L-thyroxine oral drops, solution Henning can therefore be unreservedly recommended from a clinical point of view.

Complete results of this study were published in 2004 (23) with one objective being to define the initial dosage as dosage recommendations for the initial therapy of congenital hypothyroidism (CH) in newborns vary between 8 µg/kg/d and 10-15 µg/kg/d.

Von Heppe JH et al 2004 (23)	
Design	Prospective cohort study
Patients	Twenty-eight consecutive newborns with primary CH detected in the screening program.
Sample size	n=28
Objectives	To evaluate the practicability of LT4 in liquid form and to define the initial dosage for optimal treatment.
Outcomes	TSH, T3, T4, free T3 and free T4 before therapy and during follow-up up to 2 years. After 2 years a standardized developmental test (Griffith) was performed.
Results	The median dosage at start of therapy was 12.3 µg LT4/kg/d and decreased to about 5 µg LT4/kg/d after 9 months. The median time of normalization of TSH (≤6 mU/I) was 2 weeks. In 21 patients, who received a median starting dosage of 12.7 µg LT4/kg (range 9.8-17.1 µg/kg), TSH levels normalized within a median of 1 week. Seven patients receiving only 10.1 µg LT4/kg normalized their TSH only after a median of 2 months.
Authors conclusions	The authors concluded that newborns with CH should normalize their TSH within 1-2 weeks. The initial dose necessary to normalize TSH is not lower when a liquid solution is used. The higher dose used in tablets is not due to inefficient absorption, but rather reflects the increased demand for thyroid hormone in the first weeks of life.

Assessor's comment:

There are no data submitted comparing liquid LT4 with tablets, and this is not necessary as it would be beyond the scope of this assessment. The data, however, support the notion that a higher dose in the beginning of treatment results in a faster normalisation of TSH. The dosage used is close to the dose recommended in current guidelines (10-15 µg/kg/d).

Two studies (one initial study then a follow-up study) included children with congenital hypothyroidism treated with levothyroxine using a tablet formulation:

Selva KA et al. 2002 (14)	
Design	Randomised, 12 week study
Patients	Infants of birth weight 3 to 4 kg with CH (n = 47) detected by newborn screening were randomly assigned into three L-thyroxine treatment dose arms: <ul style="list-style-type: none"> - 37.5 µg/day (group 1) - 62.5 µg/day for 3 days, then 37.5 µg/day (group 2) - 50 µg/day (group 3).
Sample size	n=47
Objectives	To determine the optimal initial treatment dose of L-thyroxine in congenital hypothyroidism (CH) by evaluating the time course of rise of thyroxine (T4) and free T4 concentrations into an established "target range" and normalization of thyroid-stimulating hormone (TSH) and to reevaluate the "target range" for T4 and free T4 concentrations during the first 2 weeks of CH treatment.
Outcomes	Serum T4, free T4, triiodothyronine (T3), free T3, and TSH were measured before treatment and at 3 days and 1, 2, 4, 8, and 12 weeks after treatment.
Results	T4 and free T4 concentrations increased into the target range (10 to 16 µg/dL) <ul style="list-style-type: none"> - by 3 days of therapy in infants in groups 2 and 3 and - by 1 week in group 1 50 µg/day (average 14.5 µg/kg/day) provided the most rapid normalization of TSH by 2 weeks. With the use of linear regression analysis of T4 versus TSH or free T4 versus TSH plots, the intercept at the lower range of normal for TSH (1.7 mU/L) showed T4 = 19.5 µg/dL and free T4 = 5.23 ng/dL.
Authors conclusions	The authors concluded that initial dosing of 50 µg/day (12-17 µg/kg per day) raised serum T4 and free T4 concentrations to target range by 3 days and normalized TSH by 2 weeks of therapy. They recommended consideration of a somewhat higher "target range" of 10 to 18 µg/dL for T4 and 2 to 5.0 ng/dL for free T4 during the first 2 weeks of L-thyroxine treatment. After 2 weeks of treatment, the target range drops to 10 to 16 µg/dL for T4 and 1.6 to 2.2 for free T4.

Selva KA et al. 2005 (15)	
Design	Randomised study, long-term (21 months – 8 years) follow-up examining neurodevelopmental outcomes in subjects from the previous study cohort (14).
Patients	Infants of birth weight 3 to 4 kg with CH (n = 47) detected by newborn screening were randomly assigned into three L-thyroxine treatment dose arms: <ul style="list-style-type: none"> - 37.5 µg/day (group 1) - 62.5 µg/day for 3 days, then 37.5 µg/day (group 2) - 50 µg/day (group 3).
Sample size	n=31
Objectives	To compare neurodevelopmental outcomes in severe and moderate congenital hypothyroidism (CH) among 3 different initial L-thyroxine doses and to examine the effect of the time to thyroid function normalization on neurodevelopmental outcomes.
Outcomes	Neurodevelopmental assessments of 31 subjects included the Mullen Scales of Early Learning, Wechsler Preschool and Primary Scale of Intelligence-Revised, Wechsler Intelligence Scale for Children, Wide-Range Achievement Test, and Child Behavioral Checklist.
Results	Subjects started on higher initial L-thyroxine doses (50 µg) had full-scale IQ scores 11 points higher than those started on lower (37.5 µg) initial doses. Verbal IQ, performance IQ, and achievement scores did not differ among the 3 treatment cohorts. Subjects with moderate CH had higher full-scale IQ scores than subjects with severe CH, regardless of the initial treatment dose. Subjects who took longer than 2 weeks to normalize thyroid function had significantly lower cognitive, attention, and achievement scores than those who achieved normal thyroid function at 1 or 2 weeks of therapy.
Authors conclusions	In authors' opinion, initial L-thyroxine dose and faster time to normalization of thyroid function are important to optimal neurodevelopmental outcome. In severe CH, it is important to choose an initial dose at the higher end of the recommended range to achieve these goals.

One Cochrane Review assessed the effects of thyroid hormones in congenital hypothyroidism:
– **Ng et al. 2009 (9)**

One of the main issues in the management of CH relates to the initial dose of levothyroxine to be used in order to achieve optimal results in terms of intellectual development. Currently, it remains unclear whether high dose thyroid hormone replacement is more effective than low dose in the treatment of CH. The objectives of this review were to determine the effects of high versus low dose of initial thyroid hormone replacement for congenital hypothyroidism.

Randomised controlled trials investigating the effects of high versus low dose of initial thyroid hormone replacement for congenital hypothyroidism were identified by searching The Cochrane Library, MEDLINE and EMBASE and reference lists of published papers.

The initial search identified 1014 records which identified 13 publications for further examination. After screening the full text of the 13 selected papers, only one study evaluating 47 babies finally met the inclusion criteria. This study was described above (14, 15). Growth and adverse effects were not reported in the included trial.

According to authors' conclusions, there is currently only one randomised controlled trial evaluating the effects of high versus low dose of initial thyroid hormone replacement for CH. There is inadequate evidence to suggest that a high dose is more beneficial compared to a low dose initial thyroid hormone replacement in the treatment of CH.

Assessor's comment:

The choice of initial dose in the treatment of CH is still a matter of some discussion; however, in current guidelines an initial dose of 10-15 µg/kg is recommended. This corresponds rather well to the higher dose intervals used in all studies described above. Both studies show similar results with normalisation of TSH within 2 weeks. The long-term data is, however, too scarce to allow any conclusions on a possible beneficial effects on neurodevelopmental outcome when using a higher dose. This is further supported by the thorough literature search done by the authors of the Cochrane review. This review only included the data published by Selva et al (14, 15).

In conclusion, the data lend some further support to the current posology in the treatment of congenital hypothyroidism but should not lead to any changes in the SPC.

Other indications

Several studies have been identified which assessed the efficacy of levothyroxin in other indications, mainly in preterm infants, but also in children with Down syndrome and in euthyroid children with type 1 diabetes and autoimmune thyroiditis.

Preterm infants:

Two main studies were included in the CO, by Vanhole et al (19), and by Van Wassenaer et al. Further, six follow-up studies of the Van Wassenaer study cohort were also included. The main features of the studies are described below.

Vanhole C et al. 1997 (19)	
Design	Randomised, placebo-controlled, double-blind study.
Patients	Preterm newborns with a gestational age <31 wk. <ul style="list-style-type: none"> - 20 infants received a daily dose of 20 µg/kg L-T4 for 2 wk, - 20 control infants receive saline.
Sample size	n=40
Objectives	To assess the endocrine and clinical effects of increasing serum T4 levels in preterm newborns. Preterm newborns have low serum thyroxine (T4) levels compared with late-gestational fetuses. Low thyroid hormone levels are associated with increased severity of neonatal illness and neurodevelopmental dysfunction.
Outcomes	Serum concentrations of T4, triiodothyronine (T3), reverse T3 (rT3), thyroglobulin (TG), and TSH were measured weekly as well as serum levels of GH, prolactin, and IGF-I. After 2 wk, a TSH releasing hormone (TRH) test was performed. Neonatal illness and outcome was evaluated by noting heart rate, oxygen requirement, duration of ventilation, development of chronic lung disease, oral fluid intake, and weight gain; a Bayley score was done at the corrected age of 7 mo.
Results	L-T4 administration induced a marked increase in serum T4 without apparent change in T3 levels, whereas the postnatal decline in serum rT3 was more gradual. L-T4 treatment was associated with a decrease in serum TG and TSH levels. TRH injection induced a definite rise in serum TSH and T3 controls, but not in L-T4 treated newborns. Neither L-T4 treatment, nor TRH administration appeared to alter circulating levels of prolactin, GH, or IGF-I. No clinical effects of L-T4 administration were detected.

Authors conclusions	The study characterized the changes that exogenous L-t4 induces in the thyroid axis of the newborn, but failed to identify any clinical benefit or adverse event. The data point to the feasibility of L-T4 administration and suggest a L-T4 dose , but does not establish the necessity of such treatment. Further studies are needed.
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Van Wassenae AG et al. 1997 (not submitted)	
Design	Randomised, double-blind, placebo-controlled L- thyroxine supplementation trial was performed in a level III neonatal intensive care unit.
Patients	Infants < 30 weeks gestation <ul style="list-style-type: none"> - a fixed dose of thyroxine (8 µg/kg birthweight/day) - placebo given during the first 6 weeks of life.
Sample size	n=200
Objectives	To study the effect of thyroxine administration on neurodevelopmental outcome in very preterm children. Thyroid hormones are essential for brain maturation. Very preterm infants, who are at risk of neurodevelopmental disabilities also have low T4 and FT4 values in the first weeks after birth. This transient hypothyroxinemia may in part be causal to the neurodevelopmental problems.
Outcomes	Mental, psychomotor and neurological developmental outcome at 2 years of age.
Results	The T4- and placebo groups were subdivided into 4 groups according to gestational age. FT4-values during the first weeks after birth were lowest in the youngest gestational age group in the T4 as well as in the placebo group. In this group with infants < 27 weeks' gestation mental developmental outcome at 2 years of age was significantly better than in the placebo group of the same gestational age. There was also a trend towards a better psychomotor and neurological outcome. Beyond 27 weeks' gestation, no clear effect of T4 could be found; on the contrary, a possible harmful effect on mental developmental outcome might be the result.
Authors conclusions	The authors concluded that T4 treatment possibly improves developmental outcome in infants < 27 weeks' gestation, but seems not necessary beyond this gestational age.

Several publications describe **follow-up results of this study**:

Briet JM et al. 1999 (not submitted)	
Design	Randomised, double-blind, placebo-controlled L- thyroxine supplementation trial was performed in a level III neonatal intensive care unit.
Patients	2-year follow-up of infants < 30 weeks gestation <ul style="list-style-type: none"> - a fixed dose of thyroxine (8 µg/kg birthweight/day) - placebo given during the first 6 weeks of life.
Sample size	n=200
Objectives	To evaluate the effect of thyroxine administration on behavioural outcome at the age of 2 years.
Outcomes	ND
Results	More externalizing, especially destructive, behaviours were found in the

	group given thyroxine than in the placebo group. This difference was more pronounced in boys and in children born after 27 weeks' gestation. The thyroxine-treated children with behavioural problems had lower plasma-free thyroxine levels than the thyroxine-treated children without behavioural problems.
Authors conclusions	According to the authors, this finding suggests that the presence of more behavioural problems in the group given thyroxine was not an immediate consequence of the treatment.

Briet JM et al. 2001 (not submitted)	
Design	Randomised, double-blind, placebo-controlled L- thyroxine supplementation trial was performed in a level III neonatal intensive care unit.
Patients	5- year follow-up of infants < 30 weeks gestation <ul style="list-style-type: none"> - a fixed dose of thyroxine (8 µg/kg birthweight/day) - placebo given during the first 6 weeks of life.
Sample size	n=157 survivors from the original cohort, 99 % participated in the follow-up
Objectives	To study the effects of neonatal T4 supplementation on outcome at early school age.
Outcomes	Standardized measurements were used to assess cognitive, behavioral, and motor outcome, as well as a qualitative assessment of neurologic functioning.
Results	Survivors of the T4 trial were assessed at the age of 5.7 years. Outcome on all domains was comparable between the T4 group and placebo group. In children <27 weeks' gestation, a 10 IQ point difference was found in favor of the T4 group, whereas in children of 29 weeks' gestation, a difference of 15 IQ points was found in favor of the placebo group. Teachers' reports showed less behavioral problems in the T4-treated children of 25/26 weeks' gestation, but more behavioural problems in the T4-treated children of 27 weeks' gestation. Differences in motor outcome and neurologic outcome were in favour of the T4-treated children <29 weeks' gestation, but not of the T4-treated children of 29 weeks' gestation.
Authors conclusions	According to authors' conclusion, they found benefits of T4 supplementation for children <29 weeks' gestation, and especially in children of 25/26 weeks' gestation. However, in children of 29 weeks' gestation T4 supplementation is associated with more developmental problems.

Van Wassenaer AG et al. 2002 (not submitted)	
Design	Randomised, double-blind, placebo-controlled L- thyroxine supplementation trial was performed in a level III neonatal intensive care unit.
Patients	5- year follow-up of infants < 30 weeks gestation <ul style="list-style-type: none"> - a fixed dose of thyroxine (8 µg/kg birthweight/day) - placebo given during the first 6 weeks of life.
Sample size	n=200
Objectives	T4 treatment was associated with better 5-year outcome in infants <29 weeks' gestation, but with worse outcome in infants of 29 weeks. The

	objectives were to assess whether these effects could be related to low, respectively high free thyroxine (FT4) levels.
Outcomes	For each infant, the average FT4 of 5 scheduled measurements was calculated between day 3 and day 28. Infants of the placebo and the T4 group separately were divided in 2 groups. The placebo group consisted of a group of infants with average FT4 in the lowest quartile and a group in the upper 75%. The T4 group consisted of a group of infants with average FT4 in the upper quartile and a group in the lower 75%. Developmental outcome (mental/cognitive, motor, and neurologic) at 2 and 5.7 years was compared between high and low FT4 groups, and then compared separately for the T4 and placebo group.
Results	In the placebo group, low FT4 was associated with worse outcome on all domains at both time points. After correction for confounding variables, mental and neurologic outcome remained significantly different at 2 years, and motor outcome at 5 years. In the T4 group, high FT4 was not associated with worse outcome, neither at 2 nor at 5 years.
Authors conclusions	The authors concluded that in untreated infants, low FT4 values during the first 4 weeks after birth in infants born at <30 weeks' gestation are associated with worse neurodevelopmental outcome at 2 and 5 years. In T4-treated infants, high FT4 is not associated with worse outcome. Other factors than high FT4 concentrations must play a role in the worse outcome of the T4-treated group of 29 weeks' gestational age.

Van Wassenaer AG et al. 2005 (22)	
Design	Randomised, double-blind, placebo-controlled L- thyroxine supplementation trial was performed in a level III neonatal intensive care unit.
Patients	10-year follow-up of infants < 30 weeks gestation - a fixed dose of thyroxine (8 µg/kg birthweight/day) - placebo given during the first 6 weeks of life.
Sample size	n=156 (113 responded, 72 %)
Objectives	T4 supplementation was associated with improved outcome of infants <28 weeks' gestation and worse outcome of infants of 29 weeks' gestation. The objectives were to study gestational age dependent effects of T4 supplementation at the mean age of 10.5 years in children participating in the randomized, controlled trial.
Outcomes	Questionnaires regarding school outcome, behaviour, quality of life, motor problems, and parental stress were sent to the parents and children and their teachers at the same time point for all surviving children (9-12 years of age).
Results	Nonrespondents had more sociodemographic risk factors and worse development until 5.5 years. At the mean age of 10.5 years, T4 supplementation was associated with better school outcome in those who were <27 weeks' gestation and better motor outcome in those who were <28 weeks' gestation, whereas the reverse was true for those who were born at 29 weeks' gestation. No other gestational age-dependent outcomes were found.
Authors conclusions	The authors concluded that gestation-dependent effects of T4 supplementation remain stable over time. These effects do not prove beneficial effects of T4 in infants <28 weeks but should be the background

	for a new randomized, controlled trial with thyroid hormone in this age group.
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Smit BJ et al. 1998a (16)	
Design	Randomised, double-blind, placebo-controlled L- thyroxine supplementation trial was performed in a level III neonatal intensive care unit. 6 month follow-up.
Patients	Infants < 30 weeks gestation <ul style="list-style-type: none"> - a fixed dose of thyroxine (8 µg/kg birthweight/day) - placebo given during the first 6 weeks of life.
Sample size	n=200
Objectives	The objective of this work was to study the effect of L-thyroxine supplementation on neurologic maturation in very preterm infants with transient hypothyroxinemia.
Outcomes	Median nerve somatosensory evoked potentials were recorded, measuring cortical N1 peak latency at 2 weeks of age, at term, and at 6 months (corrected) age.
Results	Cortical N1 peak latency was not decreased significantly in the L-thyroxine group compared with the placebo group throughout the study period.
Authors conclusions	The authors concluded that L-Thyroxine supplementation during the first 6 weeks of life did not decrease cortical N1 peak latency in infants of <30 weeks' gestational age.

Smit BJ et al. 1998b (17)	
Design	Randomised, double-blind, placebo-controlled L- thyroxine supplementation trial was performed in a level III neonatal intensive care unit. 66 weeks follow-up.
Patients	Infants < 30 weeks gestation <ul style="list-style-type: none"> - a fixed dose of thyroxine (8 µg/kg birthweight/day) - placebo given during the first 6 weeks of life.
Sample size	n=200
Objectives	Transient hypothyroxinemia is common in preterm infants and has been associated with neurodevelopmental dysfunction and slow nerve conduction velocity. The objective was to answer the question whether L-thyroxine supplementation improves motor nerve conduction velocity.
Outcomes	Motor nerve conduction velocity was measured in the ulnar and posterior tibial nerve shortly after birth, at 2 weeks, at 40 weeks, and at 66 weeks postmenstrual age.
Results	At 2 weeks, the ulnar motor nerve conduction velocity had improved in the L-thyroxine group compared with the placebo group, although the difference was not statistically significant (difference between means: 0.8 msec; 96% CI:-0.13 to 1.80; p = 0.06). Later on, no effect of L-thyroxine supplementation on motor nerve conduction velocity was found.
Authors conclusions	The authors concluded that this study shows that in infants < 30 weeks' gestational age L-thyroxine supplementation during the first 6 weeks of life does not clearly improve motor nerve conduction velocity.

Assessor's comment:

Preterm infants have been shown to have low thyroid hormone levels in conjunction with low or normal TSH levels. The main objective of both studies described above is to investigate whether levothyroxine supplementation could lead to improvements in clinical outcome and neurodevelopment. The Van Wassenaer study gives some indications that there might be a beneficial effect in the infants who were born <27 weeks of gestation, however, data are yet too scarce to support any recommendations in this patient group.

Three **Cochrane reviews** have been identified, which examined the effects of thyroid hormone therapy in preterm infants:

– **Osborn DA 2001 (10)**

Observational studies have shown an association between transiently low thyroid hormone levels in preterm infants in the first weeks of life (transient hypothyroxinemia) and abnormal neurodevelopmental outcome. Thyroid hormone therapy might prevent this morbidity. The objectives of this review were to assess whether thyroid hormone therapy in preterm infants without congenital hypothyroidism results in clinically important changes in neonatal and long term outcomes in terms of benefits and harms.

The standard search strategy of the Neonatal Review Group was used. All trials using random or quasirandom patient allocation, in which thyroid hormone therapy (either treatment or prophylaxis) was compared to control in premature infants. Primary clinical outcomes included measures of neurodevelopmental outcome and mortality.

Nine studies were identified that compared thyroid hormone treatment to control. Four randomized and one quasi-randomized study met inclusion criteria. All studies enrolled preterm infants < 32 weeks gestation, but used different timing, dose and duration of treatment with thyroid hormones. Four studies used thyroxine, whereas one study used triiodothyronine. Only two studies with neurodevelopmental follow-up were of good methodology. All studies were of small size with the largest enrolling 200 infants. Meta-analysis of five studies found no significant difference in mortality to discharge (typical RR 0.70, 95% CI 0.42, 1.17) in infants who received thyroid hormone treatment compared to controls.

Meta-analysis of two studies found no significant difference in the Bayley MDI or PDI performed at 7-12 months. One study found no significant differences in the Bayley MDI and PDI at 24 months, incidence of cerebral palsy (RR 0.72, 95% CI 0.28, 1.84), death and cerebral palsy (RR 0.70, 95%CI 0.43, 1.14) or the RAKIT IQ score (WMD -2.10, 95% CI -7.91, 3.71) at 5.7 years of age. Fraction of inspired oxygen was lower in infants receiving triiodothyronine in one small quasi-randomized study, but not in infants receiving thyroxine in a randomized study. Duration of mechanical ventilation and incidence of chronic lung disease were not reduced in infants receiving early thyroid hormone therapy.

In author's opinion, this review does not support the use of thyroid hormones in preterm infants to reduce neonatal mortality, improve neurodevelopmental outcome or to reduce the severity of respiratory distress syndrome. An analysis of data from one study which showed benefits in infants 24-25 weeks gestation was not prespecified and should be treated with caution. The small number of infants included in trials incorporated in this review limits the power of the metaanalysis to detect clinically important differences in neonatal outcomes. Future trials are warranted and should be of sufficient size to detect clinically important differences in neurodevelopmental outcomes. They should consider enrolling those infants most likely to benefit from thyroid hormone treatment such as infants born at less than 27 weeks gestation.

Assessor's comment:

The meta-analysis includes both studies previously described and the objective was to evaluate any clinically important changes in neonatal and long term outcomes in terms of benefits and harms. The conclusions of the author are supported.

– **Osborn DA et al. 2007a (11)**

Preterm infants with respiratory distress syndrome are at increased risk of adverse neonatal and developmental outcomes. In animal research, thyroid hormones stimulate surfactant production and reduce the incidence and severity of respiratory distress when given antenatally. The objectives of this review were to determine whether thyroid hormone therapy used postnatally in preterm infants with suspected respiratory distress syndrome results in clinically important improvements in respiratory morbidity and subsequent improvements in neonatal and long term outcomes. Searches were performed of The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2006), MEDLINE (1966 - March 2006), PREMEDLINE (March 2006), EMBASE (1980 - March 2006), previous reviews including cross-references, abstracts and conference proceedings, supplemented by requests to expert informants. Trials that enrolled preterm infants with suspected respiratory distress syndrome and allocated infants thyroid hormone treatment compared to control commenced in the first 48 hours after birth.

Two studies enrolled preterm infants with respiratory distress. Both studies had methodological concerns including quasi-random methods of patient allocation, no blinding of treatment or measurement and substantial post allocation losses. Neither study reported any significant benefits in neonatal morbidity or mortality from use of thyroid hormones. Metaanalysis of two studies (80 infants) found no significant difference in mortality to discharge (typical RR 1.00, 95% CI 0.47, 2.14). Amato 1988 reported no significant difference in use of mechanical ventilation (RR 0.64, 95% CI 0.38, 1.09). No significant effects were found in use of mechanical ventilation, duration of mechanical ventilation, air leak, CLD at 28 days in survivors, patent ductus arteriosus, intraventricular haemorrhage or necrotising enterocolitis. Neurodevelopment was not reported.

The authors concluded that there is no evidence from controlled clinical trials that postnatal thyroid hormone treatment reduces the severity of respiratory distress syndrome, neonatal morbidity or mortality in preterm infants with respiratory distress syndrome.

Assessor's comment:

This meta-analysis aimed at evaluating clinically important improvements in respiratory morbidity and subsequent improvements in neonatal and long term outcomes in preterm infants. Again only two studies were identified that met inclusion criteria. No effect, neither positive nor negative, was seen with regards to mortality or morbidity.

– **Osborn DA et al. 2007b (12)**

Extremely premature infants are at risk of transient hypothyroxinaemia in the first weeks after birth. These low thyroid hormone levels are associated with an increased incidence of neonatal morbidity, mortality and longer term developmental impairments. Thyroid hormone therapy might prevent these problems. The objectives of this review were to determine the evidence for thyroid hormone therapy in preterm infants with transient hypothyroxinaemia (low thyroid hormone level, normal TSH) for improvement of neonatal outcomes and neurodevelopment.

Searches were performed of The Cochrane Central Register of Controlled (CENTRAL, The Cochrane Library, Issue 1, 2006), MEDLINE (1966 - March 2006), PREMEDLINE (March 2006), EMBASE (1980 - March 2006), previous reviews including cross references, abstracts and conference proceedings, supplemented by requests to expert informants. Trials enrolling preterm infants with transient hypothyroxinaemia (low thyroid hormone level, normal TSH level) in the neonatal period, using random or quasi-random patient allocation to thyroid hormone therapy compared to control (placebo or no treatment).

Only one study was eligible which enrolled 23 infants < 1250 g and 25 - 28 weeks gestation with transient hypothyroxinaemia (serum total T4 \leq 4 μ g/dl and TSH \leq 20 IU/L). Infants were randomised to thyroxine 10 μ g/kg/day or placebo beginning on day 15 and continuing daily for seven weeks. This study reported no neonatal mortality and one infant death in each group prior to discharge. No significant difference was reported in CLD at 28 days or 36 weeks, patent ductus arteriosus, necrotising enterocolitis, retinopathy or prematurity, weight gain, growth in head circumference or length. No significant difference was reported

for mean T4 levels between thyroxine and placebo treated infants on day 21, 35, 49, 63 and 77 after birth. Free T4 was not measured. Neurodevelopmental follow up was inadequate to draw any conclusions from.

The authors concluded that there is insufficient evidence to determine whether use of thyroid hormones for treatment of preterm infants with transient hypothyroxinaemia results in changes in neonatal morbidity and mortality, or reductions in neurodevelopmental impairments. Further research is required.

Assessor's comment:

In this review only one eligible study was found, inclusion criteria being slightly different from the Cochrane review cited above, where the infants were included regardless of thyroid hormonal status. This small study could not show any effects on short-term morbidity or mortality.

Down syndrome:

Van Trotsenburg ASP et al. 2005 (20)	
Design	Single-center, randomized, double-blind, 24-month trial (enrollment June 1999 to August 2001) with nationwide recruitment.
Patients	Neonates were randomly assigned to treatment for 2 yr with either <ul style="list-style-type: none"> - thyroxine (n = 99; initial dose 8 µg/kg) - placebo (n = 97). Daily thyroxine doses were adjusted at regular intervals to maintain plasma TSH in its normal and free T4 concentrations in its high-normal range. Placebo dose adjustments mirrored those of thyroxine.
Sample size	n=196
Objectives	Young Down syndrome children appear to have a mild form of congenital hypothyroidism that is rarely detected by neonatal screening and usually left untreated. The objective of this study was to investigate the effects of thyroxine treatment on development and growth of young Down syndrome children.
Outcomes	The primary outcome was mental and motor development at age 24 months, assessed with the Bayley Scales of Infant Development II.
Results	At age 24 months, the developmental testing results of 90 thyroxine, and 91 placebo-treated children were available for analysis. The thyroxine-treated children had a 0.7-month smaller delay in motor developmental age (95% confidence interval, -1.4 to 0), corresponding to a difference of seven motor developmental index points. The mental developmental age delay was also 0.7 month smaller in the thyroxine group (95% confidence interval, -1.5 to 0.2), but lacked statistical significance. Thyroxine-treated children had greater gains in length (1.1 cm; 95% confidence interval, 0.2 to 2.0) and weight (378 g; 95% confidence interval 55 to 701).
Authors conclusions	The authors concluded that these data provide evidence to support the hypothesis that thyroxine treatment may improve development and growth of young Down syndrome children. Thyroxine treatment should be considered in Down syndrome neonates to maximize their early development and growth.

Van Trotsenburg ASP et al. 2006 (21)	
Design	Single-center, randomized, double-blind, 24-month trial (enrollment June 1999 to August 2001) with nationwide recruitment.
Patients	Neonates were randomly assigned to treatment for 2 yr with either

	<ul style="list-style-type: none"> - thyroxine (n = 99; initial dose 8 µg/kg) - placebo (n = 97). <p>Daily thyroxine doses were adjusted at regular intervals to maintain plasma TSH in its normal and free T4 concentrations in its high-normal range. Placebo dose adjustments mirrored those of thyroxine.</p>
Sample size	n=196
Objectives	The aim of this study was to determine whether thyroxine treatment would improve nerve conduction in infants with Down syndrome.
Outcomes	The outcome measures were nerve conduction velocity and central conduction time, determined through median nerve somatosensory evoked potential recording, at the age of 24 months.
Results	At the age of 24 months, somatosensory evoked potential recordings for 81 thyroxine-treated and 84 placebo-treated infants were available for analysis. Nerve conduction velocity and central conduction time did not differ significantly between the 2 treatment groups (nerve conduction velocity: thyroxine: 51.0 m/second; placebo: 50.1 m/second; difference: 0.9 m/second; central conduction time: thyroxine: 8.83 milliseconds; placebo: 8.73 milliseconds; difference: 0.1 milliseconds).
Authors conclusions	The authors concluded that postnatal thyroxine treatment of infants with Down syndrome did not alter somatosensory evoked potential measured peripheral or central nerve conduction significantly. The absence of favorable effects suggests that pathologic mechanisms other than mild postnatal hypothyroidism underlie the impaired nerve conduction. The absence of adverse effects suggests that longstanding plasma free thyroxine concentrations in the high normal range are not harmful to nerve maturation.

Assessor's comment:
Both publications cited above refer to the same study population. Some beneficial effects on motor development and growth were shown after 2 years in the primary report. These data, however, needs to be confirmed before any recommendations could be given for the treatment of paediatric patients with Down syndrome, where hypothyroidism has not been detected at screening.

Type 1 diabetes and autoimmune thyroiditis:

Karges B et al. 2007 (6)	
Design	Prospective, randomized, open, controlled clinical trial at six tertiary care centers for pediatric endocrinology and diabetes.
Patients	Of 611 children and adolescents with T1D, 89 individuals (14.5%) were identified with positive thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), or both. Of these, 30 patients (age, 13.3 ± 2.1 yr) met the inclusion criteria and were randomized to receive L-T4 (n = 16 patients) or no treatment (n = 14 patients). L-T4 (1.3 µg/kg daily) was given for 24 months in the treatment group, followed by an additional observation period of 6 months in both groups.
Sample size	n=30
Objectives	Patients with type 1 diabetes (T1D) have an increased risk of autoimmune thyroiditis (AIT). The objective was to determine whether levothyroxine (L-T4) treatment prevents the clinical manifestation of AIT in euthyroid subjects with T1D.
Outcomes	Thyroid gland volume (as determined by ultrasound), serum levels of TSH, thyroid hormones, TPOAb, and TgAb were assessed every 6 months

	for 30 months.
Results	Mean thyroid volume decreased in the treatment group after 24 months (-0.60 SD score) and increased in the observation group (+ 1.11 SD score; P = 0.0218). Serum thyrotropin, free T4, TPOAb, and TgAb levels were not significantly different in both groups during the entire study period. Hypothyroidism developed in three individuals treated with L-T4 and in four untreated patients (conversion rate, 9.3% per year).
Authors conclusions	According to authors' conclusions, in this study in euthyroid patients with AIT and T1D, L-T4 treatment reduced thyroid volume but had no effect on thyroid function and serum autoantibody levels.

Assessor's comment:

This small study failed to show any preventive effect of levothyroxine treatment, when given to T1D patients with an increased risk of autoimmune thyroiditis.

- **Safety**

Safety data from the MAH (sanofi-aventis) postmarketing experience including spontaneous direct reports from health professionals, health authorities, company partners and scientific literature reports, are included and analyzed in scheduled periodic safety update reports (PSURs). Since levothyroxine has a paediatric indication, monitoring of this special patient group was routinely conducted, and any findings were reported in the designated subsection of the PSUR.

In preparation for this expert opinion document and for identification of adverse reactions with levothyroxine use in paediatric population, Age of patients, 18-years-old or younger, was the main criteria for case identification. Per review, it appeared that the majority of the reports in children are associated with the misuse of the product including accidental exposure, intentional and unintentional overdose, and medication errors; there were also reporting lack of efficacy and report of drug exposure via parent without an adverse reaction. These cases were excluded from the safety analysis due to their nature of the reports. In addition, any duplicate cases identified from the search were also excluded.

The majority of the case reports included in this review was nonserious. Current review of the reports did not identify any safety concern associated with levothyroxine treatment in children. The reported adverse reaction(s) are likely attributed to either hypo- or hyperthyroidism in connection with change in therapeutic effect of levothyroxine. Frequent food and drug interactions and the individual condition of the patient may contribute to this phenomenon. Monitoring of clinical symptoms and thyroid function tests and adjustment of the dosage, if necessary, is emphasized in the product prescribing information.

Bone development has been considered as a monitoring parameter in children receiving treatment with levothyroxine. This potential safety risk was discussed in a literature article included with this submission. The authors concluded that long-term thyroxine therapy in children has no adverse effect on bone mineral density (18). Results of subsequent studies and publications are consistent with this conclusion.

Based on this review, levothyroxine continues to be regarded as safe replacement or supplemental therapy in children.

Assessor's comment:

The MAH's conclusion on the safety aspects when using levothyroxine in the paediatric population is endorsed.

3. Discussion on clinical aspects

MAH's conclusion on data

Levothyroxine is recommended for treating congenital or acquired hypothyroidism in children. Due to the major consequences of congenital hypothyroidism, specific guidelines have been published which provide treatment recommendations.

The clinical experience regarding efficacy of levothyroxine for treating hypothyroidism in children has been mainly acquired through retrospective studies or non randomized studies. A clinical expert report reviewing the clinical pharmacology and the efficacy data of the oral drops formulation is provided. In addition, one study including additional follow-up results compared different doses of levothyroxine in children with congenital hypothyroidism. As recently assessed in a Cochrane review, there is inadequate evidence to suggest that a high dose is more beneficial compared to a low dose initial thyroid hormone replacement in the treatment of congenital hypothyroidism.

Regarding published data in non approved indications, the benefit of levothyroxin in preterm infants with transient hypothyroxinemia or with a respiratory distress syndrome has not been demonstrated. The results obtained in Down syndrome need to be confirmed, and the potential of levothyroxine for the treatment and prevention of goiter in euthyroid children with type 1 diabetes and autoimmune thyroiditis is under debate.

According to the safety overview presented in this document, levothyroxine continues to be regarded as safe replacement or supplemental therapy in children.

In conclusion, sanofi-aventis suggests that the review of paediatric data does not implicate any changes to the SPCs currently approved in different EU countries.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

On 5th June, 2009, the Rapporteur circulated the day 70 assessment report for the EU Worksharing Procedure for paediatric data for levothyroxine, concluding that there is a need to harmonise the paediatric posology for levothyroxine. Comments were received from Member States and a List of Questions was subsequently sent to the MAH.

On 3rd September 2009, the MAH (sanofi-aventis) submitted their responses to the Request for Supplementary Information. In their response the MAH (sanofi-aventis) agreed that there is a need to harmonise the paediatric posology for levothyroxine in European countries.

Following assessment of the MAH's responses, and taking the comments from Member States into account, a final draft assessment report with a revised paediatric posology wording was circulated by the Rapporteur on 10th November 2009.

On 5th December 2009, comments were received from the Member States, where the overall conclusions had been accepted.

- Overall conclusion

Congenital hypothyroidism (CH) was first described in the late 19th century and different preparations of thyroid hormones have long been used to treat hypothyroidism. Levothyroxine has been in use for more than 50 years in the treatment of hypothyroidism in both paediatric and adult patients. There are a number of different levothyroxine products, most being nationally approved. Thus, the knowledge on how to use levothyroxine is mainly based on vast clinical experience and to some extent on retrospective studies or

non controlled trials. Since substitution with levothyroxine in hypothyroidism in paediatric patients is vital to normal development and in some cases to survival, recommendations on how to treat paediatric patients is included in most SPCs. Although differently worded, the recommendations are similar with regards to congenital hypothyroidism whereas the recommendations for treating acquired hypothyroidism differ slightly, primarily regarding which starting dose to use.

The dose recommendations for the treatment of CH are supported by clinical trials (Fisher & Foley, Paediatrics 1989; Germak & Foley, J Pediatr 1990). The same recommendations are given both by the European Society for Paediatric Endocrinology (2, 4) and the American Academy of Paediatrics (Paediatrics, 2006; 117:2290-2303). The importance of fast normalisation of thyroid status in CH to ensure normal neurodevelopment is well known, although there is still insufficient knowledge on the optimal dose regimen especially with regards to the long-term effects on growth and development.

The overview mainly deals with issues on the choice of dose in patients with congenital hypothyroidism (CH) and with the possible use of levothyroxine in other indications (preterm infants, Down's syndrome and autoimmune disease (T1D)). No new data regarding the treatment of acquired hypothyroidism have been submitted. In these cases, rapid normalisation of thyroid hormone status is not as important as in CH, therefore treatment can be started with somewhat lower doses that then are titrated until full substitution is achieved.

The safety review done by the MAH (sanofi-aventis) has not revealed any new concerns about using levothyroxine in the paediatric population.

In conclusion, the reviewed data lend support to the current posology in the treatment of congenital hypothyroidism but does not support the addition of any new information in the SPC.

The wording of the posology section, however, differs between MAHs and for the same MAH in different countries. It is therefore proposed that the wording of the paediatric posology for levothyroxine should be harmonised.

It is suggested that a common wording regarding the treatment of hypothyroidism in paediatric patients is implemented in a type II variation.

- **Recommendation**

Type II variation to be requested from the MAH within 60 days after finalising this procedure.

The following wording in section 4.2 regarding the use of levothyroxine in congenital and acquired hypothyroidism in paediatric patients is suggested:

Paediatric patients

The maintenance dose is generally 100 to 150 micrograms per m² body surface area.

For neonates and infants with congenital hypothyroidism, where rapid replacement is important, the initial recommended dosage is 10 to 15 micrograms per kg BW per day for the first 3 months. Thereafter, the dose should be adjusted individually according to the clinical findings and thyroid hormone and TSH values.

For children with acquired hypothyroidism, the initial recommended dosage is 12.5-50 micrograms per day. The dose should be increased gradually every 2 to 4 weeks according to the clinical findings and thyroid hormone and TSH values until the full replacement dose is reached.

Infants should be given the total daily dose at least half an hour before the first meal of the day.

When applicable:

Tablets are to be disintegrated in some water (10 to 15 mL) and the resultant suspension, which must be prepared freshly as required, is to be administered with some more liquid (5 to 10 mL).

Where necessary the package leaflet should be changed accordingly.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

A proposal for an updated PL should be submitted together with the updated SmPC.

VII. LIST OF REFERENCES

The list of literature references in module 5 includes:

1. Grant 1995 p85-9 - Congenital hyperthyroidism: optimal management in light of 15 years experience of screening
2. Grütters 1993 p974-5 - Guidelines for neonatal screening programmes for congenital hypothyroidism
3. Grütters 1999 - Report on clinical experience with L-thyroxine drops
4. Grütters 2007 p107-11 - Update on the management of congenital hypothyroidism
5. Hehrmann 1994 p1-11 - Iodine deficiency goiter - Drug treatment in children, adolescents, young adults and pregnant women
6. Karges 2007 p1647-52 - Levothyroxine in euthyroid autoimmune thyroiditis and type 1 diabetes: a randomized, controlled trial
7. Lafranchi 1992 p32-39 - Thyroiditis and acquired hypothyroidism
8. Monographie Levothyroxin 1990
9. Ng 2009 - High versus low dose of initial thyroid hormone replacement for congenital hypothyroidism
10. Osborn 2001 - Thyroid hormones for preventing neurodevelopmental impairment in preterm infants
11. Osborn 2007a - Postnatal thyroid hormones for respiratory distress syndrome in preterm infants
12. Osborn 2007b - Postnatal thyroid hormones for preterm infants with transient hypothyroxinaemia
13. Rogers 1994 p344-50 - Thyroid disease in children
14. Selva 2002 p786-92 - Initial treatment dose of L-thyroxine in congenital hypothyroidism
15. Selva 2005 p775-80 - Neurodevelopmental outcomes in congenital hypothyroidism: comparison of initial T4 dose and time to reach target T4 and TSH
16. Smit 1998a p865-9 - Somatosensory evoked potentials in very preterm infants in relation to L-Thyroxine supplementation
17. Smit 1998b p64-9 - Motor nerve conduction velocity in very preterm infants in relation to L-Thyroxine supplementation
18. Tümer 1999 p519-23 - Bone mineral density and metabolism in children treated with L-thyroxine
19. VanHole 1997 p87-92 - L-Thyroxine treatment of preterm newborns: clinical and endocrine effects

20. VanTrotsenburg 2005 p3304-11 - The effect of thyroxine treatment started in the neonatal period on development and growth of two-year-old down syndrome children: a randomized clinical trial
21. VanTrotsenburg 2006 pe825-32 - Median nerve conduction velocity and central conduction time measured with somatosensory evoked potentials in thyroxine-treated infants with Down syndrome
22. VanWassenaer 2005 pe613-8 - Ten-year follow-up of children born at < 30 weeks gestational age supplemented with thyroxine in the neonatal period in a randomized, controlled trial
23. VonHeppe 2004 p967-74 - The use of L-T4 as liquid solution

VIII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED OF REFERENCES

MAH	Name of the medicinal product
RHONE-POULENC RHORER PHARMACEUT	LEVOTHROID 500, 0.5 mg powder for injection
SANOFI-AVENTIS DEUTSCHLAND GMBH	L-THYROXIN HENNING 25, 25 µg tablet L-THYROXIN HENNING 50, 50 µg tablet L-THYROXIN HENNING 75, 75 µg tablet L-THYROXIN HENNING 100, 100 µg tablet L-THYROXIN HENNING 125, 125 µg tablet L-THYROXIN HENNING 150, 150 µg tablet L-THYROXIN HENNING 175, 175 µg tablet L-THYROXIN HENNING 200, 200 µg tablet L-THYROXIN HENNING TEST, 1 mg tablet L-THYROXIN HENNING INJECT, 500 µg solution for injection L-THYROXIN HENNING TROPFEN, 100 µg oral drops, solution
SANOFI-AVENTIS GmbH OSTERREICH	L-THYROXIN HENNING 25, 25 µg tablet L-THYROXIN HENNING 50, 50 µg tablet L-THYROXIN HENNING 75, 75 µg tablet L-THYROXIN HENNING 100, 100 µg tablet L-THYROXIN HENNING 125, 125 µg tablet L-THYROXIN HENNING 150, 150 µg tablet