CBG MEB

Public Assessment Report

Thyrax Duotab 0.025 mg, 0.100 mg and 0.150 mg, tablets

(levothyroxine sodium)

NL License RVG: 09334, 08389, 13683

Date: 20 August 2015

This module reflects the scientific discussion and assessment of possible adverse drug reactions associated with the change of the package of Thyrax Duotab from a glass bottle to an Alu/Alu blister package. This assessment was finalised on 30 July 2015.

I. RECOMMENDATION

Based on the review of data relating to an increase of the adverse drug reactions (ADRs) reported after a package change of Thyrax Duotab, the Medicines Evaluation Board of the Netherlands (MEB) considers that both the tablets packed in blister and bottle package meet the relevant quality requirements. However, during in-use, the blister package seems to offer a slightly more consistent protection of the tablets from conditions leading to decreased dissolution.

The Board recognises that there is a possibility that a slight adjustment in medicinal treatment of hypothyroidism may lead to clinically relevant changes of the patient's equilibrium of levothyroxine, which could possibly explain the rise in the number of ADR reports to Lareb after introduction of the blister package. However, no data are available to inform whether the observed differences in dissolution profiles between Thyrax in blister pack and bottle actually translate to increased levothyroxine blood levels.

The Marketing Authorisation Holder, Aspen Pharma Trading Limited, is required to clarify a few outstanding points in order to safeguard the quality of this medicine. The MEB and Lareb will continue to closely monitor the use of Thyrax Duotab.

II. EXECUTIVE SUMMARY

II.1 Introduction and scope of the assessment

Thyrax Duotab contains the active substance levothyroxine, which is a synthetically prepared levo-isomer of thyroxine, the major hormone secreted from the thyroid gland, and is indicated for the treatment of hypothyroidism. This medicinal product has been authorized in the Netherlands since 1980.

The change of container closure system for Thyrax Duotab from a glass bottle to an Al/Al blister was approved by the MEB as part of a grouped variation in December 2012. The variation also included a change in the analytical control methods for assay and impurities of the drug product, and in the specifications for impurities of the drug product. The composition of the tablets and the process to manufacture the tablets remained unchanged.

On 16 September 2014, the MEB received a letter from the Netherlands Pharmacovigilance Centre Lareb with an overview of reports regarding adverse drug reactions possibly associated with the recent change of the package of Thyrax. Based on these reports, the MEB decided to re-evaluate the variation and assess whether a relation could be identified between the change in packaging and the adverse events reported, as such relation was not clear at that moment.

The Marketing Authorisation Holder (MAH) was asked to provide a comparison of reporting rates for adverse events reported before and after packaging change, to investigate the root-cause of the increase in reports and to provide a risk analysis.

The MAH confirmed that no relation could be found between the adverse events reported and specific batches on the Dutch market. The bottle packaging was a multi-dose packaging whereas in the blister packaging each tablet is protected in its individual package until it is removed to be administered. Considering this difference in packaging, the MEB requested the MAH to investigate whether there is a difference in in-use stability between the product in the glass tablet container and in the blister packaging. Upon this request, the MAH provided the study results of a comparative in-use stability study, based on an acceptable protocol, which are discussed below.

In addition, Lareb published an updated analysis of cases received on their website, titled *Bijwerkingen na Verpakkingswijziging Thyrax®*, dated 3 July 2015, which was also taken into account in the assessment.

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

III.1.1 Comparative in-use stability data

Study design
The MAH submitted an appropriate in-use stability protocol, dated 12 February 2015. The comparative in-use study was started in March 2015 and performed as described in the protocol. For the initial analyses, the required amount of tablets were taken per batch. The samples were taken from one brown glass bottle and 4 Al/Al blisters per batch. The remainders of these bottles and blisters were discarded. At the initial time point, samples were stored in a stability chamber at 25°C±2°C/60%±5% RH. On each working day all bottles were opened, and one tablet was removed from each bottle to simulate the normal use of the product (weekend days excluded). The wadding filter was removed on the first day and not placed back. On time point 1, 2 and 3 months the required amount of tablets was removed from each batch of bottles and blisters for analysis. Samples were taken randomly from designated bottles and blisters according to the sampling scheme.

Study objects
Four batches were used in the in-use stability testing:

1. One batch of 0.025 mg tablets, packed in brown glass bottle
2. One batch of 0.025 mg tablets, packed in Al/Al blister
3. One batch of 0.150 mg tablets, packed in brown glass bottle
4. One batch of 0.150 mg tablets, packed in Al/Al blister

Batches were manufactured at the approved manufacturing site between August 2014 and January 2015.

Test parameters
Assay, degradation products and dissolution of the tablets were tested. The current release and shelf-life criteria for assay, related substances and dissolution are given below.

Test	Method	Release acceptance criteria	Shelf-life acceptance criteria
Levothyroxine sodium (calculated as levothyroxine)	In-house HPLC	25 (23.75-27.8) µg/tablet 95.0 – 105.0%	25 (22.5-27.8) µg/tablet 90.0 – 105.0%
Impurities	In-house HPLC		
Total degradation products		≤ 3.0%	≤ 7.0%
Dissolution rate levothyroxine sodium	USP 711	At 30 min Q = 75%	At 60 min Q = 50%

In addition to the in-house method, dissolution was tested according to the current British Pharmacopoeia (BP) method (Q = 75% at 45 minutes) and United States Pharmacopoeia (USP) method I (Q = 70% at 45 minutes). Testing time points: at start of the study and after 1, 2 and 3 months in-use.

Assay results

Time point (month)		At release	0	1	2	3
% of declaration		%	%	%	%	%
bottle	0.025 mg	102.4	101.6	97.6	102.4	100.0
bottle	0.150 mg	100.6	97.6	98.5	98.9	97.9
blister	0.025 mg	105.2	104.8	104.4	103.6	104.4
blister	0.150 mg	100.6	101.0	101.1	99.3	100.3

The assay value does not change during the in-use stability study for both the bottle and blister packaging. No difference in this quality attribute could thus be identified between products packaged in a bottle after opening or in a blister during a period of three months.

Degradation products

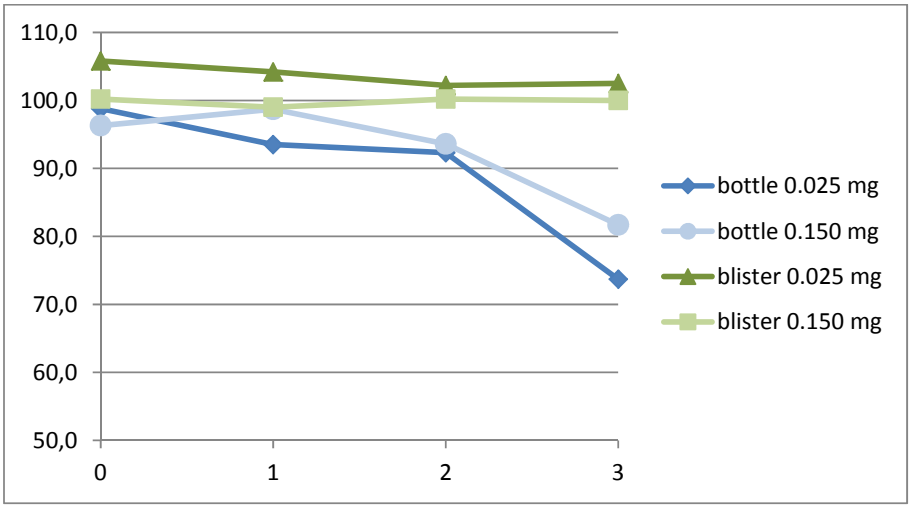
Time point (month)		At release	0	1	2	3
% total degradation		%	%	%	%	%
bottle	0.025 mg	0.2	1.3	1.5	2.1	2.9
bottle	0.150 mg	0.1	1.3	1.6	2.3	2.6
blister	0.025 mg	0.3	0.2	0.4	0.7	0.8
blister	0.150 mg	0.2	0.4	0.5	0.6	0.6

The data show that the total amount of degradation for the products packed in bottles increases by >1% during the in-use shelf-life. A smaller increase (by 0.2-0.4%) in total degradation products is observed for the products packed in the blisters. Considering the acceptance criteria for total degradation products of ≤ 7.0%, the provided results are acceptable and additional measures are not required.

Dissolution results
Dissolution by **in-house** method including the initial release value (at 60 min Q = 50%)

Time point (month)		At release			0			1			2			3			Max. Δ at 3 m
Sample time 60 min. % dissolved		%	SD	n	%	SD	n	%	SD	n	%	SD	n	%	SD	n	
bottle	0.025 mg	86.5	10.5	12	98.8	1.5	6	93.5	4.3	6	92.3	7.7	6	73.7	4.2	6	-25.1
bottle	0.150 mg	102.3	2.9	6	96.3	3.4	6	98.7	2.3	6	93.6	6.4	6	81.7	9.4	6	-14.6
blister	0.025 mg	101.3	4.2	6	105.8	2.6	6	104.2	2.7	6	102.2	2.6	6	102.5	4.7	6	-3.3
blister	0.150 mg	96.6	4.0	6	100.2	3.5	6	99.0	2.0	6	100.2	3.1	6	100.0	2.1	6	-0.2

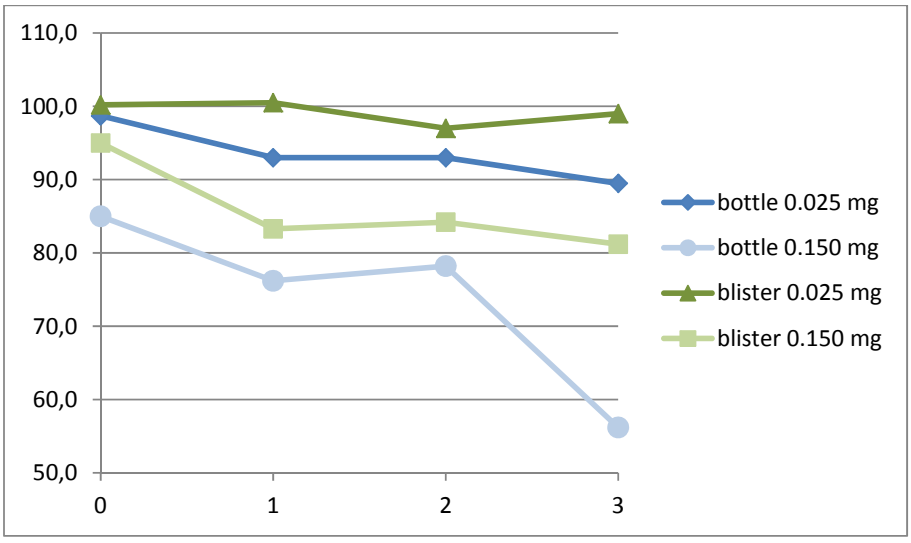
QC results in graph



Dissolution by **BP method**: Q = 75% at 45 minutes

Time point (month)		**0**			**1**			**2**			**3**			**Max. Δ at 3 m**
Sample time 45 min. % dissolved		%	SD	n	%	SD	n	%	SD	n	%	SD	n	%
bottle	0.025 mg	98.7	4.2	6	93.0	0.6	6	93.0	1.8	6	89.5	4.6	6	-9.2
bottle	0.150 mg	85.0	1.8	6	76.2	3.0	12	78.2	4.3	24	56.2	10.6	12	-28.8
blister	0.025 mg	100.2	2.8	6	100.5	1.5	6	97.0	1.4	6	99.0	2.4	6	-1.2
blister	0.150 mg	95.0	1.1	6	83.3	2.0	6	84.2	1.2	6	81.2	1.9	6	-13.8

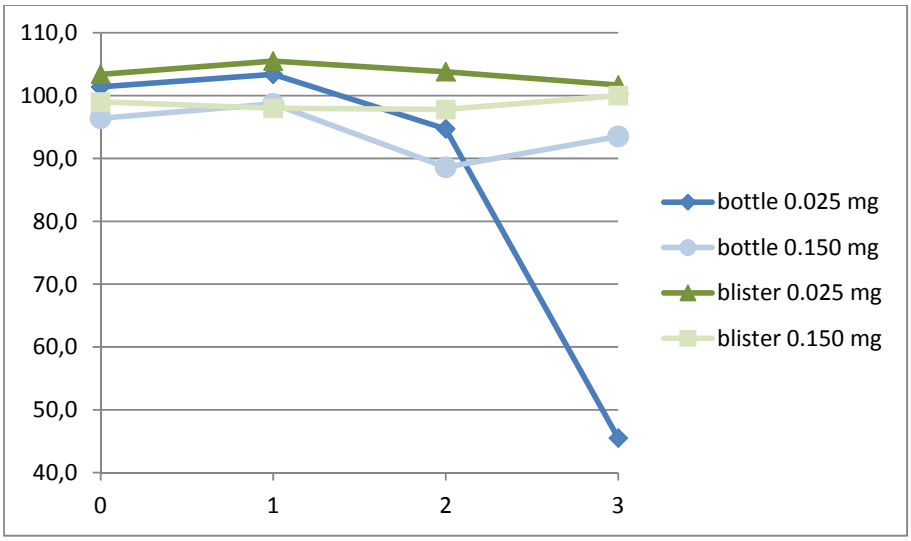
BP results in graph



Dissolution by **USP** (method 1; Q = 70% at 45 minutes)

Time point (month)		0			1			2			3			Max. Δ at 3 m
Sample time 45 min. % dissolved		%	SD	n	%	SD	n	%	SD	n	%	SD	n	%
bottle	0.025 mg	101.4	1.5	6	103.4	5.7	6	94.7	3.2	6	45.5	12.5	6	-55.9
bottle	0.150 mg	96.4	4.7	6	98.7	2.1	6	88.6	7.8	12	93.5	2.9	6	-2.9
blister	0.025 mg	103.4	2.6	6	105.5	1.4	6	103.8	1.3	6	101.7	3.0	6	-1.7
blister	0.150 mg	99.0	1.6	6	98.0	1.7	6	97.8	2.8	6	100.0	3.6	6	+1.0

USP results in graph



The tablets packaged in bottles show a decreased dissolution rate during in-use at all test conditions. The tablets packaged in blisters show a decreasing trend at most conditions. At QC and USP conditions, the absolute decrease of the dissolution at 3 months of the bottled tablets is consistently larger than that of the blistered tablets. At BP conditions this is less pronounced.

The tablets packaged in blisters comply with the respective acceptance criteria at all three test conditions. The Thyrax Duotab product in both blister and bottle complies with the current QC acceptance criteria.

The results obtained with the current BP method show that one of the batches packaged in bottles does not comply with the BP acceptance criteria. The results obtained with the USP method show that the other batch packaged in bottles does not comply with the acceptance criteria. The results are thus not consistent between the methods.

The variability of the results (expressed as standard deviation, SD) differs per method and time point. The maximum SD observed for tablets in bottles is 12.5%; the maximum SD in blisters is 4.2%.

III.1.2 In-use stability in relation to increased adverse drug reaction reports

The assay values decrease and the degradation products increase in both containers. Degradation takes place faster in the opened bottles compared to the blisters but remains well within the acceptable limit. A change in assay or impurities therefore does not seem to clarify the observed increase in patient reports at Lareb.
All six dissolution profiles of batches packaged in bottles show a larger decrease during an in-use period of 3 months than the blister batches to which they were compared. Considering the available data, during in-use, the blister package seems to offer a more consistent protection of the tablets from environmental conditions leading to decreased dissolution.
During the in-use shelf-life after opening of the bottles, the tablets may be exposed to variable environmental conditions. The blister package remains closed until the tablets are removed per unit, which keeps the environmental conditions to which the tablets are exposed more stable than in an opened bottle. The experiences reported by patients after the change in container closure system may be related to the observed difference in dissolution characteristics. However, no data are available to inform whether the observed differences in dissolution profiles between blister pack and bottle actually translate to increased levothyroxine blood levels. The causal relation to the increased number of reports at Lareb remains unclear.

III.2 Clinical aspects

Initial assessment of reporting rates before and after packaging change
The MAH was requested to provide reporting rates of each listed adverse drug reaction (ADR) (per section 4.8 of the SmPC, i.e. clinical symptoms of hyperthyreodism) before and after the packaging change in order to better assess the potential impact of packaging change on the safety profile of the product.

The data provided show that the reporting rate of 15 listed ADR (out of total 19) reported from all sources (healthcare professionals and patients) has significantly increased after the packaging change. The reporting rates of some ADRs have increased more then 10 fold with palpitations as the ADR with the highest increase of the reporting rate (0.35 versus 17.70). The reporting rate for hyperhidrosis increased from 0.18 to 14.36.

The comparison of reporting rates from medical confirmed reports showed a less pronounced, however still substantial increase in reporting after the packaging change. For instance, the reporting rate for palpitations increased from 0.21 to 5.26 and for hyperhidrosis from 0.07 to 3.83.

The MAH has noted that around the time of introducing the new packaging, a communication campaign was carried out in the Netherlands to inform GPs and endocrinologists about the packaging change of the product. In addition, patients were informed about the packaging change by means of a patient card. The MAH indicated that this campaign could have been a factor which stimulated the reporting of adverse events in the period following the packaging change.

The reporting rates of ADRs potentially indicative of hyperthyroidism have increased in both medically confirmed and patient reports. Considering that the aim of the campaign was to inform about the packaging change and that there was no request to report the adverse events, it is unlikely that the observed changes in the reporting rates (e.g., 10 fold increase for palpitations) could be explained by the campaign alone. This is supported by the fact that the increase in reporting rates was observed in medically confirmed reports as well, i.e. adverse events reported by healthcare providers, excluding the potential influence of data collected by the MAH through the patient forums. The largest increases in reporting rates were observed for palpitations, which is often one of the early signs of hyperthyroidism.

Based on the first data received, the MEB concluded that comparison of reporting rates of the adverse events potentially indicative of hyperthyroidism shows a substantial increase after the packaging change of Thyrax. Although the MAH indicated that the packaging change could have been a contributing factor leading to the reporting rates, the large differences between the reporting rates for some ADRs potentially indicative for hyperthyroidism suggest that the frequency of these ADRs might have increased after the packaging change. Therefore the MAH was required to issue a Direct Healthcare Professional Communication (DHPC) to provide doctors and pharmacists with appropriate warnings and advice in November 2014. Subsequently patients were informed by means of patient communication letter.

Assessment of updated adverse events report

Lareb presented an updated analysis of cases received in a report dated 3 July 2015 (*Bijwerkingen na verpakkingswijziging Thyrax®*, available on the Lareb website). The conclusion that some of the findings are difficult to interpret is endorsed by both the MEB and the MAH.

The most commonly reported adverse events were heart palpitations, fatigue and headache. This reported pattern represents complaints that are commonly seen in patients suffering from an overactive thyroid (hyperthyroidism), although some adverse events indicate hypothyroidism. The existence of hypo- and hyperthyroidism could not be confirmed. In a limited number (n=30) of patients with hyperthyroidic complaints laboratory values (TSH and FT_4) remained within the normal range in most cases. Other adverse events (AEs) are less clear to interpret.

All reports related to complaints that occurred after packaging change. No updated data regarding complaints experienced prior to the packaging change are discussed in the updated Lareb report on 1800 additional cases, so no in-depth comparison can be done between bottle and blister packaging.

Some patients (exact number not known) have taken the tablets from the blister and put them into the old bottle, assuming that the blister was the cause of the complaints. There were patients (8% of total number of patients who reported complaints after packaging change) who had also suffered from side effects during the use of the tablets from the bottle. 56% of the total number of patients who reported complaints after packaging change did not experience AEs during the use of the tablets from the glass bottle; 36% of the patients had experienced AEs during the dose titration phase, but not thereafter (data reported to the MEB by Lareb on 23 July 2015).

In 535 (45% of total) patients thyroid hormone levels have not been adjusted. In 428 patients (36%) the dose was decreased, whereas in 148 patients (12%) the dose was increased.
From only a limited number of reporting patients free T4 lab results were available, and data available was scattered and not always useful (e.g. due to missing relevant timepoints). In 30 patients it was found that the blood levels of free T4 were lowered, and in 40 patients it was found that the blood levels of free T4 were increased. The observed free T4 levels during the use of the tablets from the blister were however not outside the normal range, but showed an increase or decrease relative to the levels during use of the tablets in the bottle pack. No specific analysis has been done on cases where serum T4 levels were normal. In order to further elucidate the clinical relevance of the in-use quality findings, more systematic investigations in addition to spontaneous/stimulated post-marketing reporting would be required.

It is worrisome that 117 of the respondents have adjusted the Thyrax dose independently without consulting a healthcare provider.

Of the patients mentioned in the Lareb report 84% (n=1001) still had complaints at the time of the survey. No information on the time between change of the levothyroxine packaging and the time of experiencing the adverse events is given in the report.

Thyroid hormone replacement has been used for more than 100 years in the treatment of hypothyroidism, and there is no doubt about its overall efficacy. From literature it is known that in patients suffering from hypothyroidism treated under optimal conditions with any form of levothyroxine, up to 30% experience hyperthyroidism (based on laboratory values) while 5-10% has a hypothyroidism[1,2]. Also from literature it is known that the persistence of complaints even after optimal substitution is not an uncommon aspect in patients with hypothyroidism[3]. To date there are no epidemiologic data available for patients with persistent complaints after optimal substitution.
As a result of an increase in reported adverse events after switching to another levothyroxine brand, the MHRA compared dissolution profiles and concluded that those with the lowest dissolution gave rise to the increase in adverse events. Reporting decreased to the "normal" level after warnings were included in the SmPC suggesting a causal relation.

From a clinical perspective the reported adverse events in the Lareb publication can be explained by (a combination of) all three reasons mentioned above:

- Overtreatment in 30% of the patients
- Persistent complaints
- Small difference between brands leading to clinically relevant changes of the patient's equilibrium of levothyroxine

The lack of well documented laboratory values and results of physical examination (including ECG) prohibits further conclusions from a clinical perspective.

A new equilibrium is reached after approximately 6 weeks, implying that laboratory tests should not be done earlier[3]. Because the time to onset of the adverse events after switching to the blister packaging is not known, and because results of thyroid function tests were made available in only a limited number of patients, it is difficult to draw firm conclusions from a clinical perspective.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Following reports from the Netherlands Pharmacovigilance Centre Lareb indicating an increase in adverse drug reactions with Thyrax, the MEB initiated an investigation. The increase was suggested to be associated with a recent change of the package from a glass bottle to Alu/Alu blister, which required further assessment.

In the MEB Board meeting of 30 July 2015 the results of the in-use stability tests and the potential causal relation between the change in packaging and the increased reporting of adverse events was discussed. The Board considered that, based on the comparative in-use stability data presented, satisfactory stability has been demonstrated for tablets stored in both the bottle and blister packages. The amount of active substance was demonstrated to remain comparable over the storage time under in-use conditions. The dissolution rates of the blistered tablets show a smaller decrease than those of the tablets in bottles. Yet, all results remain well within specification for both packages.

Considering the available data, the blister package seems to offer a more consistent protection of the tablets during in-use from conditions leading to decreased dissolution. This might be the case because the blister package remains closed until the tablets are removed per unit, which keeps the environmental conditions to which the tablets are exposed more stable than in a bottle.

[1] John P Walsh, Dissatisfaction with thyroxine therapy — could the patients be right? Current Opinion in Pharmacology, Volume 2, Issue 6, 1 December 2002, Pages 717–722
[2] Anne R. Cappola, et al. Thyroid Status, Cardiovascular Risk, and Mortality in Older Adults. JAMA. 2006;295(9):1033-1041
[3] Wiersinga WM. Thyroid hormone replacement therapy. Horm Res. 2001;56 Suppl 1:74-81.

The Board recognises that there is a possibility that a slight adjustment in medicinal treatment of hypothyroidism may lead to clinically relevant changes of the patient's equilibrium of levothyroxine. This has been reported in patients who switched between different levothyroxine brands, and might explain the rise in the number of ADR reports to Lareb after introduction of the blister package. However, no data are available to inform whether the observed differences in dissolution profiles between blister pack and bottle actually translate to increased levothyroxine blood levels.

Considered all data presently available, the MEB and Lareb agreed to continue their close monitoring of Thyrax Duotab. The MAH Aspen Pharma Trading Limited is required to present an additional response to a few outstanding questions.

In short, the MAH needs to discuss the observed results in the context of the increased number of reports. The dissolution test method and drug product release and shelf-life specification should be reconsidered, in order to establish whether the quality specifications are stringent enough for this type of medicine.

The additional data will be assessed once available, and presented in the next update of this Public Assessment Report.