

Overview of reports of adverse drug reactions associated with changes of the package of Thyrax[®] (levothyroxine) from a bottle to a blister

Introduction

The drug Thyrax[®] (levothyroxine) was granted marketing authorization in the Netherlands on 6 June, 1980. Levothyroxine is a synthetically prepared levo-isomer of thyroxine, the major hormone secreted from the thyroid gland, and is indicated for the treatment of hypothyroidism [1].

End of 2013, the packaging of the Thyrax[®] had been changed from a bottle to a blister. Levothyroxine has a complex stability profile and is sensitive to various environmental factors such as light, air, and humidity [2]. In the blister package they are better protected against these environmental factors. According to the Marketing Authorization Holder (Aspen Pharma) the formulation of the product has not been changed.

Reports

From 11 April 2014 until 29 September 2014 the Netherlands Pharmacovigilance Centre Lareb received 46 reports considering possible adverse drug reactions associated with changes of the package of Thyrax[®] from the bottle to the blister. See also Table 1.

Discussion

The SmPC of Thyrax[®] described that symptoms of 'hyperthyroidism' may occur if the dosage of levothyroxine is too high or is increased too rapidly [1]. More than half of the 46 patients experienced complaints that could possibly be explained by a (rapid) dosage increase. Reactions that were reported are among others: hyperhidrosis, tremor, palpitations and abdominal discomfort. In only one patient (AE) tests actually revealed a high T4 concentration. After reduction of the dose the complaints were recovering.

Levothyroxine is sensitive to environmental factors. It may be possible that the tablet in the bottle package, over time, contained a lower dose of levothyroxine compared to tablet in the blister package, due to environmental factors. This may explain the above described reactions.

Twelve patients experiences reactions as itchy rash, pruritus and urticarial. Five patients experienced weight gain. Since the formulation of the product has not been changed, these reactions are difficult to explain. It is important to take into account the possible effect of psychological factors on the occurrence of the reactions. *Dunne et al.* explored patients perceptions on generic medicines [3]. Their study demonstrated that almost one-quarter of patients included in their study held the view that generics were of poorer quality than originators, while 18% expressed the opinion that generics do not work as well as originator products.

The Netherlands Pharmacovigilance Centre Lareb had telephone contact with the Marketing Authorization Holders of Thyrax[®]. They explained that they are exploring the problem.

Table 1. Reports adverse drug reactions associated with changes of the package of Thyrax® from a bottle to a blister

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset after package changes, Action with drug outcome	Total duration of Thyrax® use
A 173224 F, 51-60 Pharmacist	Thyrax® (levothyroxine) Hypothyroidism		hyperhidrosis, tremor,	10 days, dose not changed not recovered	1 year
B 174313 F, unknown Consumer received through the MAH	Thyrax® (levothyroxine)		palpitations, insomnia	unknown dose not changed not recovered	
C 177050 F, 41-50 Pharmacist	Thyrax® (levothyroxine)		itchy rash	1 week, drug withdrawn, unknown	years
D 177145 F, 41-50 Consumer received through the MAH	Thyrax® (levothyroxine)		lactose intolerance, hypersensi- tivity reaction	7 days, not reported, unknown	10 years
E 177916, F, unknown Consumer received through the MAH	Thyrax® (levothyroxine)		cancer, drug dose omission, inappropriate dose of drug administration	unknown, not reported, unknown	
F 178536 F, 71 years and older Pharmacist	Thyrax® (levothyroxine) Hypothyroidism	valsartan, simvastatin	fatigue, arthralgia	unknown, dose not changed, recovering	11 years
G 178964 F, 71 years and older Pharmacist	Thyrax® (levothyroxine)		pruritus, hot feeling in hand, abnormal vision, hair loss, head pressure	7 days, dose not changed, not recovered	
H 179492 M, 31-40 Consumer	Thyrax® (levothyroxine) Hypothyroidism		muscle spasm	7 days, dose not changed, not recovered	10 years
I 179588 F, 31-40 Consumer	Thyrax® (levothyroxine) Hypothyroidism		fatigue aggravated	3 weeks, not reported, not recovered	

J 179644 F, 21-30 Consumer	Thyrax® (levothyroxine) Hashimoto's thyroiditis		palpitations, sleep problem, dizziness, nausea	3 hours, dose not changed, not recovered	
K 179651 F, 41-50 Consumer	Thyrax® (levothyroxine) Hypothyroidism		arrhythmia, nausea	days, dose not changed, not recovered	3.5 year
L 179692 F, 61-70 Consumer	Thyrax® (levothyroxine) Hypothyroidism		sweating, fatigue, burning eyes, rash, abdominal discomfort, palpitations	3 weeks, not reported, not recovered	7 years
M 179705 M, 51-60 Pharmacist	Thyrax® (levothyroxine) Hypothyroidism		pruritus	unknown, dose not changed, recovering	7 years
N 179835 F, 21-30 Consumer	Thyrax® (levothyroxine) Hashimoto's Thyroiditis	mirtazapine, venlafaxine	light headedness, fatigue, nausea	1 days, dose not changed, not recovered	
O 179910 F, 31-40 Consumer	Thyrax® (levothyroxine) Hypothyroidism		myalgia, palpitations, fatigue, pruritus	3 weeks, dose not changed, not recovered	
P 179921 F, 31-40 Consumer	Thyrax® (levothyroxine) Hypothyroidism		breast pain, short of breath, eye disorder	4 weeks, dose not changed, not recovered	2 years
Q 180050 F, 71 years and older Pharmacist	Thyrax® (levothyroxine) Hypothyroidism		sweating, gastrointestinal disorder, headache	unknown, not reported, not recovered	4 years
R 180080 F, 31-40 Consumer	Thyrax® (levothyroxine) Hypothyroidism		allergy, fatigue, weight increased	days, dose not changed, not recovered	3 years
S 180123 F, 51-60 Consumer	Thyrax® (levothyroxine) Graves' disease	verapamil, solifenacin	tenseness, body fluid retention, rash, nervousness, heavy feeling in legs, eyes tearing, dizziness	days, dose not changed, not recovered	12 years
T 180268 M, 61-70 Consumer	Thyrax® (levothyroxine) Hypothyroidism		difficulty sleeping, myalgia, constipation	2 days, dose not changed, not recovered	4 years
U 180403 F, 31-40	Thyrax® (levothyroxine) Hypothyroidism		fatigue	3 days, dose not changed, unknown	

V 180404 F, 61-70 Consumer	Thyrax® (levothyroxine) Hypothyroidism	nifedipine, citalopram	depressed mood, arrhythmia cardiac, headache, general malaise, hyperhidrosis	2 days, dose not changed, not recovered	years
W 180405 F, 41-50 Consumer	Thyrax® (levothyroxine) Disorder thyroid		fatigue, weight gain, dyspnoea, mood swings, arthralgia, body temperature fluctuation, constipation	7 days, drug withdrawn, not recovered	
X 180411 F, 31-40 Consumer	Thyrax® (levothyroxine) Thyroid disorder		urticaria, upper abdominal pain, eye pain, fever, constipation, palpitations, dyspnoea	7 days, not reported, not recovered	
Y 180476 F, 51-50 Pharmacist	Thyrax® (levothyroxine) Hypothyroidism		fatigue, nausea	1 day, drug withdrawn, not recovered	2 months
Z 180486 F, 31-40 Consumer	Thyrax® (levothyroxine) Thyroid disorder	ethinylestradiol/ drospirenon	fatigue, irritability, chest pain, headache	1 day, dose not changed, not recovered	
AA 180553 F, 71 years and older Pharmacist	Thyrax® (levothyroxine) Hypothyroidism		itchy rash	4 weeks, not reported, unknown	
AB 180556 F, 41-50 Pharmacist	Thyrax® (levothyroxine) Hypothyroidism		weight gain, unrest	2 weeks, not reported, unknown	
AC 180690 F, 41-50 Physician	Thyrax® (levothyroxine) Hypothyroidism	budesonide, dextran/hypromellose eye drops	palpitations, restlessness, abnormal stools, nausea	1 month, dose reduced, not recovered	3 years
AD 180744 F, 51-60 Consumer	Thyrax® (levothyroxine) Disorder thyroid	venlafaxine	upper abdominal pain, palpitations, urticarial, emotional reaction, runny nose, dry eyes, malaise	2 hours, drug withdrawn, recovered	
AE 180762 F, 51-60 Consumer	Thyrax® (levothyroxine) Hashimoto's thyroiditis	simvastatin	palpitations, dyspnoea, near fainting	3 months, dose reduced, recovering	
AF 180935	Thyrax®		weight gain	1 month,	12 years

F, 51-60 Consumer	(levothyroxine) Hashimoto's thyroiditis		(5kg), pruritus, constipation, headache	dose not changed, not recovered	
AG 181108 M, 61-70 Consumer	Thyrax® (levothyroxine) Hypothyroidism		dizziness, tinnitus, fatigue, diarrhoea	hours, not reported, not recovered	14 years
AH 181191 F, 71 years and older Physician	Thyrax® (levothyroxine) Thyroid disorder		fatigue, reaction to drug excipient, extrasystoles, oedema	days, dose no change, not recovered	
AI 181290 F, 31-40 Consumer	Thyrax® (levothyroxine) Thyroid disorder	calcium carbonate, colecalfiferol	fatigue, weight gain, mood swings	1 month, not reported, not recovered	5.5 years
AJ 181411 F, 51-60 Consumer	Thyrax® (levothyroxine) Thyroid carcinoma	propranolol, formoterol, budesonide, omeprazole	headache, muscle discomfort, fatigue, insomnia	4 weeks, dose reduced, not recovered	14 years
AK 181442 M, 61-70 Pharmacist	Thyrax® (levothyroxine) Thyroid disorder	metoprolol, flecainide	headache, low back pain	days, dose increased, not recovered	
AL 181579 F, 41-50 consumer	Thyrax® (levothyroxine) Graves' disease		myalgia, gastrointestina l discomfort, sweating, blurred vision, depressed mood, fatigue	3 days, Dose no change, not recovered	16 years
AM 181703 F, 51-60 Consumer	Thyrax® (levothyroxine) Hypothyroidism		fatigue, hyperhidrosis, muscle spasms, myalgia	3 weeks, not reported, not recovered	3 years
AN 181710 F, 41-50 Consumer	Thyrax® (levothyroxine) Hypothyroidism		myalgia, dry eyes, alopecia, sweating, sleep disturbed, fatigue	4 weeks, not reported, recovered	Positive rechallenge
AO 181713 F, 31-40 consumer	Thyrax® (levothyroxine) Hashimoto's th yroiditis	omeprazole, paroxetine	throat tightness, dyspnea, hair breakage, loss of energy	2 weeks, Dose no change, not recovered	
AP 181756 F, 41-50 consumer	Thyrax® (levothyroxine) Hashimoto's thyroiditis		myalgia, headache, fatigue	5 days, not reported, not recovered	1 year
AQ 181757 F, 61-70	Thyrax® (levothyroxine)	pantoprazole, sotalol,	nausea, head pressure,	weeks, dose not	20 years

consumer	Hypothyroidism	paracetamol, tramadol, liothyronine	sweating, fatigue	changed, not recovered	
AR 181760 F, 41-50 consumer	Thyrax® (levothyroxine) Hypothyroidism	sumatriptan	TSH increased, oedema, fatigue	2 weeks, dose not changed, not recovered	3 years
AS 181901 F, 41-50 consumer	Thyrax® (levothyroxine) Thyroid function decreased	nebivolol	urticaria, blurred vision, myalgia, constipation, fatigue	weeks, not changed, not recovered	32 years
AT 181963 F, 51-60 Consumer	Thyrax® (levothyroxine) Hypothyroidism		cardiac arrhythmia, mood change	weeks, not reported, not recovered	9 years

Additional information: Report (AP) test results: TSH 0.03, T4 16.

References

1. Dutch SmPC Thyrax®. (version date: 2014, access date: 10-9-2014) <http://db.cbq-meb.nl/IB-teksten/h08389.pdf>.
2. Collier JW, Shah RB, Gupta A, Sayeed V, Habib MJ, Khan MA. Influence of formulation and processing factors on stability of levothyroxine sodium pentahydrate. AAPS.PharmSciTech. 2010;11(2):818-25.
3. Dunne S, Shannon B, Dunne C, Cullen W. Patient perceptions of generic medicines: a mixed-methods study. Patient. 2014;7(2):177-85.

This signal has been raised on November 2014. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbqmeb.nl