The Eltroxin formulation change

An analysis of reports received by CARM

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Background

The manufacturer of Eltroxin introduced a new formulation of their product in New Zealand in July 2007 which was in line with their actions in other international markets. The changed formulation resulted in a larger white tablet which was not intended to be split and therefore no longer had a break-line requiring that where part tablet doses were prescribed that a revised dosing regimen algorithm was to be followed. The old formulation was a smaller yellow tablet that had a break-line. The excipients in the new formulation were altered, but were of types that are widely used in a diversity of other products and by other manufacturers. The active ingredient, levothyroxine, remained identical although the package and documentation for the new formulation referred to 'levothyroxine' compared to the old formulation that listed 'thyroxine'. Although the prescribing data for both formulations advised administration on an empty stomach, the promotional material for the new formulation emphasized this recommendation.

The new formulation apparently began to be distributed to pharmacies from approximately September 2007 and increasingly became the dispensed formulation as the old stocks were used up.

CARM received the first report of a problem attributed to the new formulation on 8th October 2007 and by 31st August 2008 CARM had received 663 reports of which 576 have been fully processed into the CARM database. 622of the reports were received following printed and television media coverage of patients concerns which was published around mid-June 2008.

Prior to October 2007, CARM had received 14 reports where thyroxine was the suspect agent. In 4 instances it was the sole suspect agent. These 14 reports date back to the first in 1973 which was followed by single reports every 2-3 years after 1984, with the most recent before the formulation change being October 2006.

Reports relating to formulation change

General observations

The reports implicating the formulation change describe mostly symptoms that could be attributed to thyroid dysfunction, particularly events that could be of the "hypothyroid" type. Although events have been consistently reported over the full duration of time, the later reports which represent the greatest proportion, have also described symptoms that are not consistent with thyroid dysfunction and can be grouped into the following fairly distinct categories: Conjunctivitis, Eye pain, Headache, Hypersensitivity events, Visual disturbances and Acute upper gastro-intestinal symptoms.

Although the greatest proportion of reports came from patients, reports from both patients and health professionals consistently documented similar scenarios. A consistent narrative in the reports describes the onset of unexplained and out of character symptoms in patients who had either hitherto been symptom free, or without the specific reported symptoms. They describe the diagnostic difficulty in finally arriving at the point of attributing causality to Eltroxin - only eventually occurring in some instances after extensive investigation and/or on the basis of the temporal association being the only relevant factor. Importantly, for many patients it appears that considering the potential role of thyroid medication was not initially contemplated because they had been stable on their doses over many years and even decades. In the more recent reports GP's had included historical thyroid blood levels that documented a hypothyroid picture following the change-over to the new formulation.

The patient narrative accounts are interesting for the manner in which there is consistency in the types of symptoms experienced. Considering the potential for media priming, there was a general absence of stock words or phrases that would suggest a simple recounting of heard or read terms, phrases or accounts. Instead, some patients went to extensive lengths to describe

their symptoms that left little doubt about the reality of those events for them which were then distilled into WHO-ART reaction terms by CARM. Consequently any similarity to some of the media description of events is due to this coding highlighting the reality of these event terms. Indeed in some patients the impact of the symptoms was of such a nature to result in an impact on their ability to continue with their usual daily lives, in some instances to the point of compromising work performance or abandoning longstanding activities. Other reports describe considerable inconvenience and costs that have been incurred by patients who have undergone extensive investigations, including MRI and Gastroscopy, before eventually concluding that the formulation change is the most likely factor.

Analysis of Eltroxin reports

The attached tables and figures describe the reports received by CARM from 8th October 2007 to a data lock point of 31st August 2008 during which period 576 reports were processed out of a total of 663 received.

Figure 1 illustrates that reports were received from across New Zealand. Although the distribution roughly reflects that of the population, in the first weeks, Southland reflected a disproportionate excess considering the relatively smaller population in that region. This was likely to be due to the efforts of the local newspaper highlighting the initial greater awareness of the issue. Although the proportion for this area has declined somewhat as other areas have increased, it is still relatively high. The relatively low proportion of reports from the Wellington region is not in keeping with the roughly similar proportions from the other main centers. Overall, almost half of the reports were from patients themselves, mostly following media coverage, whilst pharmacists accounted for a smaller proportion of reports (18%) compared to general practitioners (35%) as illustrated in Figure 2. In the last 6 weeks there has been a slight decrease in the proportion of pharmacist reports compared to GP origin reports, whilst the proportion from patients has remained constant.

The age and gender distribution of reports are skewed to the elderly with a mean age of 61 years (Table 3), with the greatest proportion in the range 30 to more than 80 years of age. There is a very marked female disproportionality as is illustrated in Figure 3.

Although many of the reaction terms coded related to symptoms that could be ascribed to the effects of hypothyroidism (see 'case definition' - Table 4), it was evident that other groups of symptoms were also reported that were not related to thyroid dysfunction. Table 5 lists the reaction terms according to the clusters of related symptoms that were observed. Table 5 also lists the actual number of occurrences for each of the reaction terms within the various groupings. These groupings have been used to analyse the Eltroxin reports by various patient and report parameters reflected in Table 6.

"Thyroid" symptoms

The reports describing hypothyroid-type symptoms account for the greatest proportion (53%) of all reports received for Eltroxin since the formulation change. The onset of these symptoms reflected their insidious nature based on the patient accounts with an onset within the first month. However, in many instances reporters were unclear as to the precise time at which the symptoms began, often referring to "several months", whilst some also indicated that symptoms occurred sequentially and progressively over that time. The few reports that did document thyroid function tests indicative of hypothyroidism added objectivity to the hypothyroid symptoms reported in many patients. Interestingly, whilst in some cases the thyroid levels were still within the acceptable limits, some reflected a tendency towards the limits (upper TSH or lower T4) and away from a fairly stable baseline. Not described in the table are the occasional reports documenting palpitations and diarrhoea that could be considered indicative of hyperthyroidism. This would be in keeping with the few isolated reports of TSH decreased or elevated T4. However, overall the picture in the thyroid symptoms group is predominantly one of hypothyroid findings.

Hypersensitivity events

As more reports were received it was evident some patients were also experiencing hypersensitivity-type symptoms which were manifest as events affecting the skin such as rash and pruritus – which in some patients also included itchy and red eyes, with others reporting more profound allergic reactions such as angioedema and even anaphylactic events. These events typically had a shorter duration to onset of the order of days and in some reports the dechallenge improvement or recurrence on rechallenge added weight in support of a causal association.

There are 2 reports that describe serious anaphylactic-type reactions: One is an MAH report describing an "anaphylactic reaction, swollen tongue, tongue spasm, choking sensation, 'reaction to excipients' ". A markedly elevated TSH of 43 was also documented in the narrative. The patient also had a background of allergy to sulphonamides. The events were reported as resolved on discontinuation of Eltroxin. A second report from a GP concerns a patient with Periorbital Oedema/Anaphylaxis who recovered on dechallenge.

Eye and Vision problems

Eye problems were reported frequently and consisted of 3 main sub-groups of symptoms: Red eyes/Conjunctivitis/Dry eyes (also in the hypersensitivity symptom group above), Eye pain; and disturbances of vision - often reported to be blurred vision. The eye pain is typically and fairly consistently described as severe in the back of the eye that in some reports was also associated with conjunctivitis-like symptoms. The visual problems have been described as incapacitating to the point that patients had resorted to having their refraction checked, but many reporting that there was no need for new prescriptions. One report described an exacerbation of previously well controlled glaucoma. Table 6 shows that these eye/vision symptoms were also of relatively early onset within the first weeks following the change of formulation.

Headache

The onset of headache-like symptoms shortly after changing formulation was also notable for the frequency with which they were reported (29%). They were occasionally severe or occurred with eye pain and/or the conjunctivitis group of symptoms.

Acute upper-Gastro Intestinal symptoms

The onset of acute upper gastro-intestinal symptoms were, as in the case of the hypersensitivity group, reported as an early onset event, but were particularly notable for their even earlier onset within the first days after the change-over.

Whilst the hypothyroid group of symptoms could be explained in terms of altered thyroid functioning and the hypersensitivity groups of events potentially reflecting individual sensitivity to some component of the new formulation, the visual, acute upper GI and headache-like symptoms are without obvious explanation. In some of the acute GI symptom reports patients had reported that these occurred when they followed the advice to take the tablet on an empty stomach. Unfortunately most GI reports are not sufficiently clear to add more confidence to an association with administration advice. In 403 reports Eltroxin was the sole medication mentioned.

Dosing

There was no apparent difference in symptom groups across the dosing spectrum (Table 6). However, this aspect was complex to extract, record and analyse as patients frequently (and often inadequately) described their administration regimen so that determining a daily dose or tablet form (50/100µg) was unreliable. Nevertheless, reports were grouped into those who appeared to take the same daily doses every day compared to those who used complex regimens (alternate days or different doses on different days). This analytical strategy presumed that the changeover to the revised dosing advice may have resulted in compliance problems

that could have contributed to symptoms, but no obvious pattern was apparent. Indeed 83% of reports concerned patients who were regularly taking the same daily dose suggesting that new dosing compliance advice may not be implicated..

There is clear evidence from the narrative of the reports that some patients had successfully overcome their hypothyroid symptoms through re-titrating their doses upwards, often by minute amounts. This process has typically been described as a tedious undertaking but provides evidence in support of the notion that for some patients the new formulation does not represent the same bioavailability as the old formulation that they had been stable on often for considerable time.

Outcome and Dechallenge data

Table 6 reflects that for the majority of reports the patients are still continuing their medication, although in many instances this is not specifically stated and surmised on the basis of the narrative of the report that implies that cannot do without their medication.

The reports of dechallenge improvement are important in helping to support a causal association. In 92 reports patients reported improvement on discontinuing the new formulation - either completely stopping the use of thyroxine supplementation, or in some instances moving to alternate products. These alternate products included returning to the "old formulation" in the earlier period when supplies could still be sourced; a change to the "Goldshield" brand of Eltroxin, or in some instances to the use of "whole thyroid extract". These dechallenge improvements were particularly notable in those in the acute upper GI, and Hypersensitivity report groups.

There are 30 reports describing recurrence of symptoms on rechallenge after they had resolved when the medication had been discontinued. These were particularly notable in the Hypersensitivity and GI groups of symptoms, supporting a strong causal association for these reaction groups with the new formulation of Eltroxin.

Reports with serious outcomes

Reports where Hospitalisation resulted

There were 8 reports where hospitalisation resulted. In 1 report (of MAH origin) the patient was hospitalised due to cardiac symptoms that were investigated further. The report described "circulatory collapse", memory impairment and atrial fibrillation. Three reports were from Health professionals reporting: 1 = "vomiting /collapse/unconsciousness", 2 = Tachycardia, hyperthyroid, FT4 elevated/TSH decreased and 3 = "found to be hyperthyroid and drug reduced". The four other reports were of patient accounts that they had been hospitalised: 1 = reports the patient had chest pain, palpitations and "tingling eyes". 2 = Severe dizziness /tiredness and nausea investigated with gastric biopsy and MRI, 3 = headache/dizziness/vision disturbance/hyponatremia, and 4 = Vision/Palpitation/Headache/Diarrhoea/Memory loss that had proved to be a diagnostic difficulty.

Life threatening events

There were 2 reports in this group that have already been described under the hypersensitivity group of reactions above.

> "There are 2 reports that describe serious anaphylactic-type reactions: One is an MAH report describing an "anaphylactic reaction, swollen tongue, tongue spasm, choking sensation, 'reaction to excipients' ". A markedly elevated TSH of 43 was also documented in the narrative. The patient also had a background of allergy to sulphonamides. The events were reported as resolved on discontinuation of Eltroxin. A second report from a GP concerns a patient with Periorbital Oedema/Anaphylaxis who recovered on dechallenge."

Emergency Care

There were 6 reports where patients presented themselves to emergency care/A&E. One reported “vomiting /collapse/unconsciousness”. The second reported arthralgic and hypothyroid symptoms that were incapacitating for the patient who presented to A&E on a number of occasions in desperation for relief. The remaining 3 reports describing A&E attendances were for Palpitations, disturbed sleep, tremor and diarrhoea; Rash, conjunctivitis, migraine and weight increase; and Palpitation, headache, amnesia, disturbed sleep and restlessness.

Experiences from other National Monitoring Centres Internationally

A recent request for feedback from the other 83 national monitoring centres who participate in the WHO Programme for International Drug Monitoring on their experiences either with the new Eltroxin formulation or for any experiences that might help to shed further light on the issue was distributed. Three countries responded, two of which indicated that although they didn’t have the GSK brand registered in their countries, had either observed similar reports as described in the NZ reaction groupings referred to above as reactions with the use of various levothyroxine products registered, or had observed some of the reactions arising from patients changing between local brands. Neither had experienced large numbers of reports as in the New Zealand experience to date. The third country response asked for further clarification of the bioequivalence testing process. These few responses suggest that the scale of this problem appears to be unique to New Zealand and that the specific reactions observed have been attributed both to the product as well as a consequence of change of levothyroxine brand.

Summary/Conclusion

A number of patients have reported experiencing problems when changing over to a new formulation of Eltroxin which with the exception of unremarkable excipient changes and tablet presentation is identical to its old formulation. Reports have increased in frequency in recent months possibly due to the increasing scarcity of the old formulation, but potentially intensified by the increased publicity about patient experiences. A large proportion of reports describe events with insidious onset that are compatible with hypothyroid-like symptoms that can potentially be explained on the basis of reduced individual bioavailability. Other reports such as those describing earlier onset hypersensitivity-type events suggest that the new formulation may contain constituents to which individuals have sensitivity. It is possible that another group of symptoms – those acutely affecting the upper GI tract may be related to administration on an empty stomach, but there is only limited evidence from reports that may support this possibility and so the mechanism for this group of symptoms is not entirely clear. Of more concern are the groups of symptoms relating to eye, headache and visual problems. These symptoms are at this stage without explanation, although the single report of glaucoma recurrence with the new formulation may provide some supportive evidence that links these entities in some related manner.

Although the vast majority of the reports received by CARM followed media attention which could be claimed to have influenced the motivation and particularly the content of reporting, the volume of reports that are consistent for the symptoms documented in a diversity of individual styles attests to the reality of these symptoms not only for the patients themselves, but that a real issue is apparent.

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Table 1: Geographic distribution of patients

Geographic region	Number	Percentage
Northland	16	2.8
Auckland	91	15.8
Waikato	42	7.3
Bay of Plenty	77	13.4
Gisborne	2	0.4
Hawkes Bay	16	2.8
Taranaki	4	0.7
Wanganui	4	0.7
Manawatu	20	3.5
Wairarapa	3	0.5
Wellington	33	5.7
Nelson	10	1.7
West Coast	4	0.7
Canterbury	81	14.1
South Canterbury	15	2.6
Otago	50	8.7
Southland	62	10.8
Unknown	46	8.0
Totals	**576**	100.0

Figure 1: Distribition of Eltroxin reports by region

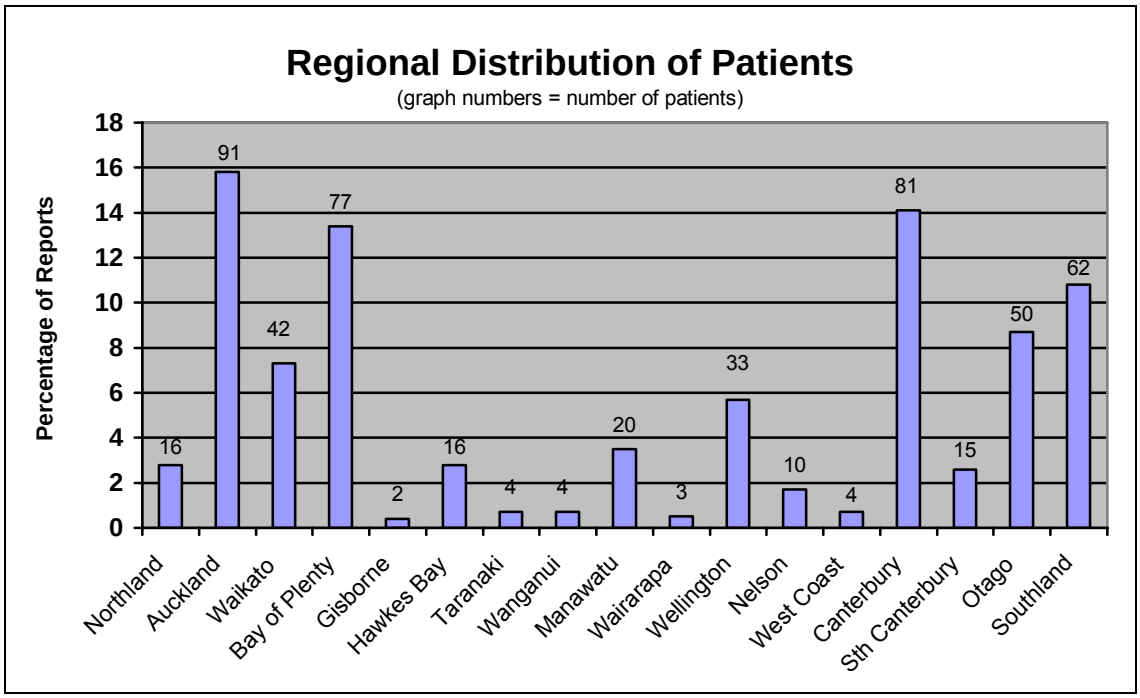

Table 2: Source of Eltroxin Reports

Description	Number	%
General Practitioners	201	34.9%
Hospitals	1	0.17%
Pharmacists	104	18.1%
Industry	24	4.2%
Other (patients, family members)	246	42.7%

Figure 2: Distribution of Eltroxin reports by source

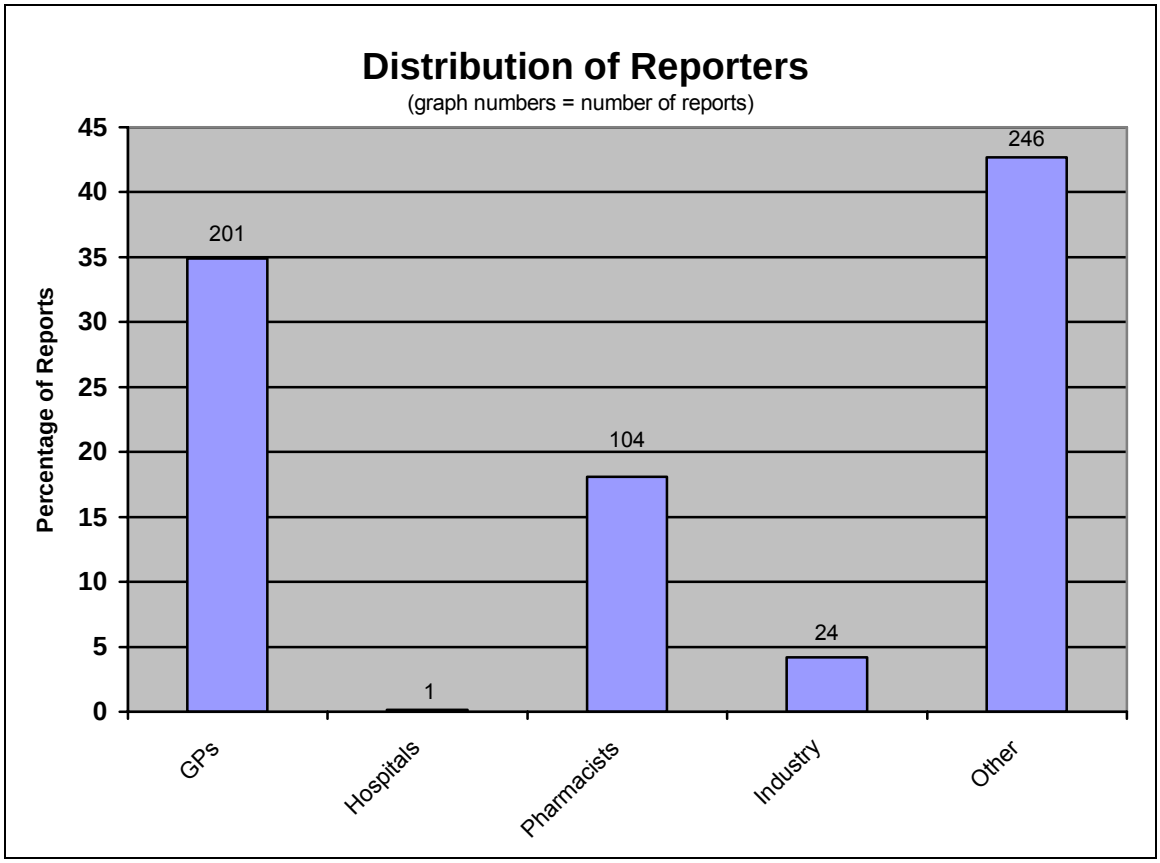

Table 3 : Age and gender distribution of Eltroxin reports

Age group	Females % of Females	Males % of Males	Total % of Cohort
Under 20	3 0.6	2 3.7	5 0.9
20 - 29	6 1.2	1 1.9	7 1.2
30 - 39	22 4.2	6 11.1	28 4.9
40 - 49	74 14.2	8 14.8	82 14.2
50 - 59	96 18.5	10 18.5	106 18.4
60 - 69	143 27.5	17 31.5	160 27.8
70 - 79	105 20.2	6 11.1	111 19.3
80 plus	40 7.7	0	40 6.9
Unknown **	31 6.0	4 7.4	37 6.4
Total	**520** 90.3	**54** 9.4	**576** 100.0

** Unknown includes 2 patients of unknown gender
Mean Age 60.7
Median 62

Figure 3: Frequency distribution of Eltroxin reports by Age and Gender

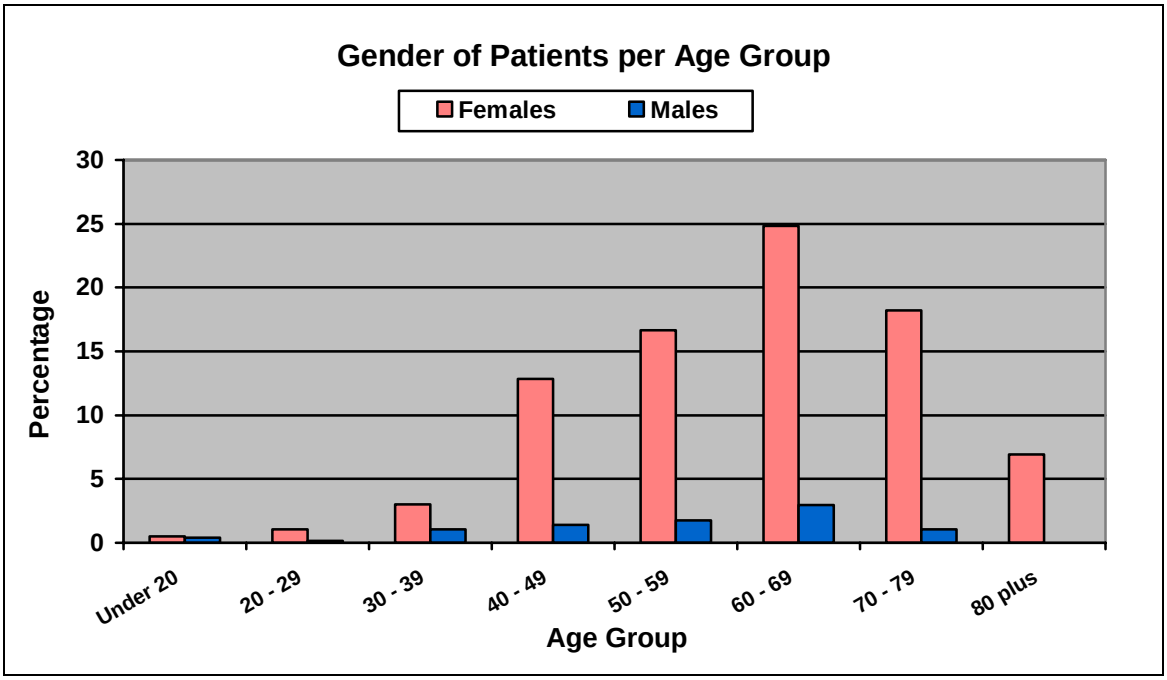

Table 4: Case definition for the hypothyroid group of symptoms

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Medical Encyclopedia: Hypothyroidism

URL of this page: http://www.nlm.nih.gov/medlineplus/ency/article/000353.htm (accessed 11/07/2008)

Risk factors include age over 50 years, female gender, obesity, thyroid surgery, and exposure of the neck to X-ray or radiation treatments.

Symptoms

Early symptoms:

- Weakness
- Fatigue
- Cold intolerance
- Constipation
- Weight gain (unintentional)
- Depression
- Joint or muscle pain
- Thin, brittle fingernails
- Thin and brittle hair
- Paleness

Late symptoms:

- Slow speech
- Dry flaky skin
- Thickening of the skin
- Puffy face, hands and feet
- Decreased taste and smell
- Thinning of eyebrows
- Hoarseness
- Abnormal menstrual periods

Additional symptoms that may be associated with this disease:

- Overall swelling
- Muscle spasms (cramps)
- Muscle pain
- Muscle atrophy
- Uncoordinated movement
- Absent menstruation
- Joint stiffness
- Dry hair
- Hair loss
- Drowsiness
- Appetite loss
- Ankle, feet, and leg swelling
- Short stature
- Separated sutures
- Delayed formation or absence of teeth

References AACE Thyroid Task Force. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Evaluation and Treatment Of Hyperthyroidism and Hypothyroidism. *Endocr Pract*. 2002;8 (6).

Table 5 : Reaction terms grouped by related symptoms

Acute Upper GI		Hypersensitivity		Conjunctivitis/ Eye		Vision		Headache		Hypothyroid		Lab	
Abdominal pain	8	Anaphylactic Rxn	1	Blepharitis	2	Vision abnormal	30	Headache	156	Alopecia	18	T4 decreased	10
Abdominal cramp	6	Anaphylaxis	1	Conjunctival Hx	5	Vision blurred	59	Migraine	9	Hair texture abnormal	1	TSH increased	37
Bloating	2	Angioedema	1	Conjunctivitis	80	Vision decreased	2			Hair disorder	1		
Dyspepsia	14	Asthma	1	Dry eyes	10	Visual disturbance	14			Nail disorder	1		
Dysphagia	1	Bronchospasm	1	Eye pain	67	Glaucoma aggr.	1			Cognitive function abn	4		
Eructation	1	Chest tightness	1	Glaucoma aggr.	1					Concentration impaired	15		
Gastro Reflux	6	Choking	1	Photophobia	12					Confusion	7		
Glossitis	1	Coughing	7	Xeropthalmia	1					Disorientation	2		
Nausea	72	Conjunctivitis	80							Depersonalisation	1		
Vomiting	17	Dry eyes	10							Thinking abnormal	7		
		Dyspnoea	6							Depression	31		
		Eczema	2							Emotional lability	3		
		Erythema nodosum	1							Mood disorder	6		
		Face oedema	2							Mood swings	4		
		Lip swelling	1							Amnesia	1		
		Oedema periorbital	6							Memory disturbance	2		
		Macular rash	2							Memory impairment	18		
		Paraesthesia	10							Memory loss	8		
		Pruritus	21							Feeling cold	11		
		Rash	17							Peripheral coldness	3		
		Rash maculopapular	1							Temp change sensation	2		
		Rash pruritic	6							Asthenia	1		
		Skin exfoliation	1							Fatigue	26		
		Sinusitis	4							Lethargy	52		
		Throat irritation	3							Malaise	4		
		Throat tightness	3							Muscle weakness	11		
		Throat swelling	1							Somnolence	9		
		Urticaria	4							Tiredness	59		
		Xeropthalmia	1							Amenorrhoea	1		
										Weight increase	66		
										Constipation	11		
										Oedema	2		
										Peripheral oedema	7		
										Carpal Tunnel Syndrome	1		
										Taste perversion/Metallic	3		
										Hyponatraemia	2		
										Hypothyroidism	11		
										Therapeutic effect decrease	13		
										Therapeutic resp.inadequate	4		
										T4 decreased	10		
										TSH increased	37		

					Arm pain	1	
					Arthralgia	47	
					Arthritis	3	
					Arthritis aggr.	6	
					Back pain	4	
					Cramps leg	1	
					Muscle spasticity	1	
					Muscle stiffness	2	
					Leg pain	2	
					Myalgia	57	
					Pain in limb	1	
					Pain neck/shoulder	2	
					Skeletal pain	4	

Table 6 : Analysis of Eltroxin reports received by CARM - 08 October 2007 to 31 August 2008

	TOTAL Reports	Acute Upper GI	Hyper-sensitivity	Conjunctivitis/ Eye	Vision	Headache	Hypothyroid	Labs
Reactions	576	110 19.1%	161 28.0%	158 27.4%	106 18.4%	165 28.6%	364 53.2%	45 7.8%
Sole Medicine	403	72	113	113	70	116	251	25
Onset								
≤ 24 hours	37	16	10	10	3	10	16	1
< 1 week	48	10	16	12	8	15	26	1
< 1 month	103	16	26	19	20	24	66	9
< 3 months	33	3	11	13	6	6	29	6
> 3 months	31	4	7	12	9	8	19	3
Not indicated	324	61	91	92	60	102	208	25
Dose indicated	451	89	124	115	75	129	285	40
Whole tabs daily	373 82.7%	75 84.3%	104 83.9%	99 86.1%	59 78.7%	106 82.2%	229 80.3%	30 75.0%
Combination regimen	78	14	20	16	16	23	56	10
Dechallenge indicated	520	102	151	149	88	149	333	44
Improved on stopping	92	29	29	21	16	25	54	3
Not improved on stopping	4	1		1		3	2	
Stopped – unknown	49	9	15	14	5	11	31	3
Medicine continued	375	63	107	113	67	110	246	38
Rechallenge recurrence	30	14	5	2	3	6	16	2
Serious	16							
Hospitalised	8							
Life threatening	2							
Emergency care	6							