

Eltroxin – Summary of reports received by CARM

CARM now holds a significant number of reports relating to the change to the new formulation of Eltroxin since it was increasingly dispensed from around October 2007. From October to around June 2008 CARM had received around 40 reports with an increase in numbers following initial and ongoing media attention which started in June 2008.

Although many of these reports describe symptoms that may be related to altered thyroid functioning, symptoms and signs fall into roughly three groups: About half of the reports included events that suggest that some patients absorb less levothyroxine from the new tablets (reduced bioavailability) with emergence of hypothyroid-type symptoms such as lethargy, tiredness, weight gain, memory disturbances and mental processing problems, muscle weakness and muscle and joint pains. More recently these reports have also described changes in thyroid function tests supportive of hypothyroidism. A second group of reports have documented blurred vision, headaches, eye pain or eye discomfort - with or without accompanying itchy eyes. The third group comprises events that appear to be of an allergic nature with events such as rash, urticaria/hives and angioedema.

For many patients these events have evolved insidiously since the change over to the new formulation. At times only after extensive investigation and elimination of other potential causes has it been established that the formulation change is the likely factor. It is evident from these reports that for some patients the consequences of these events have had significant personal, social and lifestyle impact.

Although the active component in the new formulation is now listed as levothyroxine, this is just a more precise name for “thyroxine” which was listed on the old formulation. The new formulation contains exactly the same active component as the old formulation did and is still manufactured by the same company. The new formulation differs in that it is now a white tablet, the break line is no longer present and there are different excipients. The company has apparently made this change internationally and this product, which is now manufactured in Germany, has already been in use in other countries for almost 2 years.

Recent reports to CARM have observed that despite long-term stability on the old formulation, some patients have benefitted from dose adjustments according to their thyroid function tests to achieve optimal dosing on the new formulation. This suggests that for some patients the new formulation may not be as bioavailable as the old formulation. Although regular monitoring of thyroid function on thyroid replacement therapy is considered standard practice, when unexpected symptoms present it becomes particularly important to monitor TSH levels to determine if dose adjustment may be required. Due to the long half life of this medication the effects of dose adjustments are unlikely to be observed before 4-5 weeks. This can therefore be a tedious process and enough time should be allowed for the dose adjustment to manifest effects before a further adjustment is made. However, the positive experiences of some patients following dose adjustment/titration provide reassurance that the troublesome hypothyroid-group of symptoms can be overcome.

At present, the Glaxo Smith Kline product (Eltroxin) is the only formulation that is registered and the company is no longer manufacturing the older formulation previously used in New Zealand. Some pharmacists have independently imported and dispensed alternative non-registered products such as the “Goldshield Eltroxin” that patients have been able to access with variable success and at their own expense. Reports received by CARM indicate that patients changing to this brand have reported alleviation of symptoms in all 3 groups described earlier. It is also important to note that for some patients the change has not been as positive.

Medsafe – the Ministry of Health Agency concerned with drug regulation has received regular CARM updates and analyses on the emerging problem and has from an early stage initiated a number of actions to further investigate and identify a potential cause. All investigations to date have not identified any aspect of the new formulation that could account for the number of events being reported. Feedback from specific requests to other countries for their experiences reveals that these events are without precedent elsewhere. This particular formulation of Eltroxin manufactured in the same German plant is distributed in a number of other international markets, none of which have observed an increase in adverse event reports. In some countries the product has been available for nearly 2 years.

Medsafe and PHARMAC announced on 11 September 2008 that following Medsafe’s longstanding appeal encouraging additional suppliers of Thyroxine to register products, that two applications have now been received. Abbott Laboratories has submitted an application for their product (Synthroid) – which had also recently become one of the alternative unregistered products that pharmacists could access from their usual sources. Goldshield Healthcare NZ has also submitted an application for their “Eltroxin” product which is the one that had been a popular alternative referred to earlier. It is our understanding that these applications are to be processed as rapidly as possible.

It is important to note that any change of brand will still need careful monitoring and dose adjustment and it is possible that patients may experience other adverse events on changing to another formulation.

The document “Eltroxin Media Releases 080911.pdf” contains the combined Medsafe “Media Release” and “Media Conference Information” released on 11 September 2008. (Please note that since the media release, the reference therein to the intended application from Goldshield Healthcare NZ has apparently now been received.)

Media Releases

Eltroxin

11 September 2008

The Ministry of Health's drug regulatory arm Medsafe and Government drug-funding agency PHARMAC are well advanced in their efforts to source an alternative brand to the funded thyroid medicine Eltroxin.



Medsafe Group Manager Dr Stewart Jessamine says on September 3, Medsafe received its first application to seek approval for another brand of levothyroxine and he has been assured that an application for a second alternative is due to be submitted in the next week.

PHARMAC Funding and Procurement Manager Steffan Crausaz says PHARMAC will be able to give an update on funding an alternative within the next two weeks.

Since May of this year, when the numbers of adverse reactions to Eltroxin began to significantly increase, Medsafe has been contacting manufacturers and distributors of medicines encouraging them to submit an application for alternative brands of levothyroxine. "While any new products will still need to meet the required standards of safety, quality and efficacy before they can be approved, Medsafe will fast track the assessment of any applications it receives for levothyroxine to allow an approved alternative to be made available as promptly as possible," Dr Jessamine said.

Steffan Crausaz says approval by Medsafe is only the first step in the process of making a funded alternative to Eltroxin available and PHARMAC expects to complete negotiations with at least one of the alternative medicine supply companies shortly.

PHARMAC has been holding discussions with suppliers in parallel with Medsafe's work, and once a medicine has Medsafe approval, PHARMAC is well placed to move quickly on funding, says Steffan Crausaz.

"We need to be assured that sufficient stock will be available, and to consult with suppliers and the public on the listing arrangements."

Dr Jessamine says in the meantime the advice received from specialist endocrinologists is that many of the adverse reactions are consistent with some patients absorbing lower amounts of levothyroxine from the new tablets. In their expert experience, blood tests to check the level of thyroid hormone stimulating hormone (TSH), and adjustment of the dose of Eltroxin, either to increase the dose (or in some cases to decrease it) will lead to resolution of the patients symptoms over a few weeks to months. Patients taking Eltroxin who are worried about the product, or who have already changed to other brands of unapproved levothyroxine, should contact either Healthline on 0800 611-116 or their doctor, as they may need ongoing thyroid blood monitoring and dose adjustment.

Dr Jessamine confirmed the results of independent testing of both the old and new formulation of Eltroxin by ESR indicate the new Eltroxin tablets are acceptably potent and do not contain unexpected or excessive impurity content, compared to the old formulation, and meet the requirements for dissolution (a marker for how quickly the products dissolve). The batches of products tested include samples obtained from a pharmacy and from Eltroxin manufacturer GlaxoSmithKline (GSK).

Dr Jessamine says some of the claims being circulated about the product are wrong, such as:

- it is not manufactured in India
- its manufacture does not involve any genetic engineering
- it does not contain MSG or any products not found routinely in other medicines.

The active ingredient (levothyroxine) in the new formulation is made in Austria by the same company, using the same method at the same site as the old formulation, and the finished product is manufactured in Germany. The other ingredients of the new formulation are routinely found in a range of other medicines and are not associated with increased rates of adverse effects.

The new GSK formulation of Eltroxin is currently marketed in close to 30 countries around the world. Medsafe has sought information from several of these countries where they have comparable adverse reactions reporting systems to New Zealand and it is clear they are not receiving increased numbers of reports for the new formulation product.

Medsafe also asked each of the 83 countries who make up the World Health Organisation Adverse Reactions Reporting System for any information they had on increased rates of reporting to GSK Eltroxin, or to adverse reactions following switches to brands of levothyroxine. The only positive feedback received came from the United Kingdom and Australia, countries where the GSK brand of Eltroxin is not available, who reported that they have small numbers of reports of adverse reactions that are similar in nature to those received in New Zealand but associated with patients shifting between different brands of levothyroxine.

While most patients (approx 99%) continue to have no major problems with the GSK Eltroxin, many of the side effects reported by the 800 individuals who have submitted reports to the New Zealand Pharmacovigilance Centre would be explained by changes in how these individuals absorb, metabolise or excrete the new formulation of Eltroxin compared to the old product.

Dr Jessamine says that while changing to a new levothyroxine product may resolve some of the problems where the person is allergic to, or intolerant of, the new formula of Eltroxin, patients will still need to have their blood tests monitored and it is quite likely that they will need to have the dose of any new brand of product adjusted to suit their individual metabolism. If patients wish to avoid adverse effects associated with increased or decreased thyroid activity that can occur following a switch in brands, so careful monitoring and dosage is essential.

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BACKGROUND

Hypothyroidism

Thyroid medicines contain the active ingredient levothyroxine – a thyroid hormone.

Levothyroxine is used to treat hypothyroidism, a disease in which the thyroid gland is underactive and does not produce enough thyroxine, a hormone, which is important for controlling your metabolism.

Symptoms of hypothyroidism include tiredness, muscle weakness, cramps, feeling the cold, a slow heart rate, dry and flaky skin, hair loss, a deep husky voice and weight gain.

Children and elderly people usually need a smaller dose because they are more sensitive to the effects of levothyroxine.

Many people need treatment with levothyroxine long term.

Levothyroxine is produced in tablet form. Tablets are swallowed whole with a glass of water. Tablets are taken on an empty stomach, 30 minutes before breakfast.

Rare reactions to levothyroxine include:

- Diarrhoea
- Vomiting
- Palpitations (irregular heartbeat)
- Chest pain
- Sweating/flushing
- Weight loss
- Muscle weakness/cramps, tremors
- Rapid breathing
- Fever
- Headache
- Inability to sleep
- Feeling restless/excited

Many of these side effects often disappear when the dose is adjusted (lowered).

Patient advice:

Medsafe advises patients taking thyroxine to follow the dose instructions carefully and to contact their pharmacist or GP to discuss any concerns or questions they may have about this medicine.

Medsafe encourages GPs and pharmacists to review how patients are taking this medication, to monitor the effects of the change to the new formulation and to report any side effects, including problems with maintaining adequate control of hypothyroidism, to the New Zealand Pharmacovigilance Centre at the University of Otago. It is important that patients who report any adverse effects have their blood tests checked at the time of reporting. Most reports received so far have not included information about blood test results.

Although the new formulation of Eltroxin has been approved as safe and effective by Medsafe; prescribers, pharmacists and patients need to bear in mind that each individual may respond differently to the new formulation and that patients taking it should be monitored by a health professional and dose adjustments made if necessary. Patients should also make sure

they are taking their medication on an empty stomach and are taking whole tablets in accordance with the advice from their GP.

The Medsafe data sheet on Eltroxin is available here:

[http://www.medsafe.govt.nz/Profs/Datasheet/e/Eltroxin\(new\)tab.htm](http://www.medsafe.govt.nz/Profs/Datasheet/e/Eltroxin(new)tab.htm)

Testing

Testing by ESR has confirmed that Eltroxin contains nothing other than ingredients specified on the label:

- Levothyroxine sodium hydrate
- Magnesium stearate
- Microcrystalline cellulose
- Pregelatinised maize starch
- Purified talc
- Silicon dioxide

GSK no longer manufactures the formulation of levothyroxine previously sold in NZ, and no changes in formulation are planned.

The GSK brand of levothyroxine has been the only brand of product available and supplied in New Zealand for a number of years.

Prescribers can source thyroxine medicines direct from overseas under an exemption of the Medicines Act, but the medicines sourced this way have not been assessed or funded and require informed consent from patients.

GlaxoSmithKline's contact details are as follows:

GlaxoSmithKline NZ Limited
AMP Centre
Cnr Albert & Customs Streets
Private Bag 106600
Downtown
Auckland
NEW ZEALAND
Telephone (09) 367 2900
Facsimile (09) 367 2506

ENDS

For further information, please contact Michael Flyger (MoH Media Advisor) 04 496 2265 / 0274 346 878

Media Conference Information

11 September 2008

Background Information

Levothyroxine is the active ingredient present in Eltroxin tablets. Levothyroxine is a synthetically manufactured thyroid hormone used in the treatment of patients who suffer from hypothyroidism (low thyroid hormone levels). Levothyroxine is classed as a medicine with a narrow therapeutic index and hence prescribers are expected to monitor patients closely if it becomes necessary to switch a patient to a new brand or formulation.



There are approximately 70,000 patients taking Eltroxin in New Zealand.

In July 2007, the manufacturer of Eltroxin tablets (GlaxoSmithKline) introduced a new formulation of the product and stopped making the formulation previously supplied in New Zealand. Although the change occurred in July 2007, supplies of the old formulation were slowly used up by pharmacies meaning patients may not have been dispensed the new formulation until the end of 2007 or even early 2008. GlaxoSmithKline (GSK) made the decision to change the formulation. This was not due to a request from Medsafe or PHARMAC.

The new formulation contains an identical active ingredient (thyroxine also known as levothyroxine). Some of the excipients contained in the tablet have changed; however these are all commonly used in other medicines.

Medsafe evaluated the new formulation of Eltroxin against internationally accepted criteria and found that this product met all quality, safety, and bioequivalence requirements before it was given Ministerial consent.

Reports of adverse reactions

As at 2 September 2008, the Centre for Adverse Reactions Monitoring (CARM) had received 746 adverse reaction reports associated with the new formulation of Eltroxin. This figure equates to reports from approximately 1% of all patients being treated with Eltroxin in New Zealand.

Typical adverse reactions reported to CARM include:

- Symptoms that occur after use for several weeks or months that can be attributable to thyroid dysfunction such as headache, weight gain, lethargy, alopecia, insomnia, and palpitations
- Symptoms reported shortly after patients change brands of levothyroxine such eye pain, conjunctivitis, headaches, and visual disturbance
- Allergic reactions such as rash, facial oedema, and angioedema.

Medsafe has investigated adverse reaction patterns in other countries supplying the new Eltroxin formulation (e.g. Germany, the Netherlands, and Singapore). To date, these countries have not experienced an increase in adverse reactions to the new formulation as seen in New Zealand. Medsafe also contacted all 83 countries on the WHO adverse reactions monitoring scheme, seeking information on adverse reaction patterns for levothyroxine. There were no reports of increased rates of adverse reactions to the GSK brand of Eltroxin. However, Australia and the United Kingdom, countries in which the GSK brand is not available, have informed Medsafe that they have reports of adverse reactions of a similar nature to all three classes of adverse reactions described above, submitted when patients changed brands of levothyroxine. These reports are in keeping with what can be expected with a narrow therapeutic index product such as levothyroxine.

Medsafe consulted expert endocrinologists in June 2008, and again in August 2008, to discuss the adverse reactions reported to CARM. They advised that the adverse reactions described are most likely due to patients absorbing lower amounts of levothyroxine from the new tablets. In their experience blood tests to check the level of thyroid hormone stimulating hormone (TSH), and dose adjustment either to increase the dose (or in some cases to decrease it) lead to resolution of the patients symptoms over a few weeks to months. These experts endorsed Medsafe's continuing to give advice to healthcare professionals to check the patient's thyroid function tests and adjust the dose if required.

Medsafe actions and decisions

The following timeline details key Eltroxin decisions and actions taken by Medsafe.

Date	Decision/Action
March 2004	GlaxoSmithKline (GSK) submits an application to Medsafe to change the formulation of Eltroxin tablets. GSK has been the sole supplier of levothyroxine in New Zealand for at least 10 years. Medsafe evaluates the new formulation of Eltroxin against internationally accepted criteria for quality, safety, and bioequivalence.
November 2006	The new formulation of Eltroxin tablets is approved for use in New Zealand. Medsafe directs GSK to advise healthcare professionals of the change in formulation, prior to its distribution in New Zealand.
14 June 2007	GlaxoSmithKline (GSK) notifies all New Zealand GP's and pharmacies of the new formulation. The notification recommends thyroid function monitoring and dose adjustment when necessary.
29 June 2007	GSK again notifies all New Zealand GP's and pharmacies of the change in formulation. This information contains advice on dose regimen and administration and includes a resource so patients can identify the new and the old tablets.

July 2007	<p>GSK begins supplying the new formulation of Eltroxin tablets to New Zealand.</p> <p>The tablet bottles contain the wording, “New Formulation”, which is clearly visible to pharmacists. The tablets dispensed to patients are also a different colour and size to the old formulation tablets.</p> <p>Supplies of the old tablets were slowly used up by pharmacies meaning most patients did not receive the new formulation until late 2007 or early 2008.</p>
June 2008	<p>An increase in adverse reactions to the new formulation (43 to mid-June 2008) is identified by CARM. In response Medsafe:</p> <ul style="list-style-type: none"> • Re-assesses the new formulation and confirms that it meets all international standards for quality, safety, and bioequivalence • Obtains batch information from GSK for all batches supplied in New Zealand • Seeks adverse reaction data from other countries where the new formulation has been introduced. To date, an increase in adverse reactions has not been seen in Germany, the Netherlands, and Singapore. • Requires GSK to notify all New Zealand GP’s and pharmacies of the change for a third time. The public are notified directly (18 June 2008) via advertisements in national newspapers. • Requests GSK to investigate the availability of alternative Eltroxin formulations. GSK are not prepared to provide New Zealand with an alternative formulation of Eltroxin tablets. According to GSK, the previous formulation of Eltroxin is no longer manufactured. • Initiates independent testing with ESR, to rule out contamination or a poor quality product • Consults with expert endocrinologists. Medsafe is advised that most ADR’s are likely due to a lack of (or inappropriate) thyroid function monitoring and dose adjustment. • Releases advice to all New Zealand GP’s, specialists, and pharmacies emphasising the need for thyroid function monitoring and dose adjustment (27 June 2008)
July 2008	<p>GSK provides re-test results to Medsafe</p> <ul style="list-style-type: none"> • Preliminary results from all batches supplied in New Zealand indicate that the level of active ingredient and impurities are within the approved limits •
August 2008	<p>ESR provides independent test results to Medsafe</p> <ul style="list-style-type: none"> • Preliminary results from all batches supplied in New Zealand indicate that the level of active ingredient and impurities are within the approved limits • Preliminary results are comparable with GSK’s re-test results <p>Medsafe consults further with expert endocrinologists</p> <ul style="list-style-type: none"> • Medsafe provides an update on adverse reaction reports and symptoms • Advice from the endocrinologist’s remains consistent with the advice

given in June 2008.

BPAC Article

- Medsafe releases further information to healthcare professionals in conjunction with BPAC^{NZ}, by publishing an article in the *Best Practice Journal*. The article includes advice on thyroid function monitoring, dose adjustment, and access to alternative brands via the Section 29 exemption to the Medicines Act.

Access to alternative brands

- Currently, Eltroxin is the only brand of levothyroxine tablets with Ministerial consent for distribution in New Zealand. Any alternative brand can only be supplied as an unapproved medicine using an exemption provision in the Medicines Act (Section 29)
- Medsafe, in conjunction with PHARMAC, discusses the submission of applications for alternative brands supplied by Goldshield and Abbott.
- Abbott submits an application for consent to distribute an alternative formulation of levothyroxine tablets (2 September 2008).

Bioequivalence

How bioequivalence is determined

Bioequivalence is determined by comparing, as a ratio, the rate and extent of absorption, metabolism and excretion (plasma profile) of two medicines into the body. Medsafe evaluated the new formulation of Eltroxin against internationally accepted criteria for quality, safety, and bioequivalence.

Any brand or formulation change can affect the bioavailability of a medicine (how a medicine is absorbed, metabolised and excreted). As the assessment of bioequivalence is based on population statistics, even where bioequivalence is proven for two medicines, it is possible that a small proportion of patients may experience either an increased or decreased therapeutic effect when changed from one product to another. This occurs because of an individual's variability in how the medicine is absorbed, metabolised, and excreted.

For medicines that have a wide therapeutic index, i.e. the safety and efficacy of the product remains unchanged across a broad range of plasma levels of the medication, the effect of individual variability on bioavailability is likely to be unnoticeable and very few patients will report adverse effects.

For medicines that have a narrow therapeutic index (as with levothyroxine), small changes in its bioavailability may alter the plasma levels leading to either decreased or increased therapeutic effect. This means that it is expected that a small number of patients treated with levothyroxine will invariably notice an increased or decreased therapeutic effect.

The purpose of most bioequivalence trials is to compare a formulation of a medicine (i.e. a generic medicine) with an unknown efficacy profile, against a medicine, which has already been approved as both safe and effective on the basis of clinical trial data. It is internationally accepted that demonstration of bioequivalence is an acceptable surrogate for performing full clinical trials. Conducting a bioequivalence trial is significantly cheaper and quicker than performing a full clinical assessment on the new product and is favoured amongst generic medicine manufacturers.

Bioequivalence data are generated from small clinical trials using a statistically significant sample of participants. In these trials participants receive samples of each medicine in a random sequence. After receiving each medicine, blood samples are taken from participants for a sufficient period of time that a profile of the drug's absorption and elimination can be obtained. Statistical profiles of the two medicines are then compared for each trial participant.

Three metrics are compared: Cmax ratio (the maximum level of drug in the body); AUC ratio (Area Under Curve – this is a measure of the total dose absorbed and eliminated by the participant), and Tmax (the time to maximum drug concentration).

Bioequivalence is required to be determined and expressed statistically. This is due to the inherent variability of drug absorption between individuals. This variability is handled statistically by summing the blood results obtained for each of the two medicines from each individual and comparing the means and distribution of Cmax, AUC, and Tmax. When the data are assessed in this way they can be deemed to be representative of the entire population.

By international definition two medicines are considered bioequivalent if: the ratio of the Cmax and AUC ratios lies within the range of 80% and 125% at a 90% confidence level, and the difference in Tmax is not of concern clinically. It is important to note that even when a medicine meets the statistical requirements for bioequivalence there will still be a portion of the population whose individual variability falls outside the normal distribution.

Bioavailability of the new formulation of Eltroxin

GSK provided a bioequivalence study to support the clinical safety and effectiveness of the new formulation of Eltroxin. This study compared the new formulation of Eltroxin against a formulation of Eltroxin currently marketed in Europe and previously registered in New Zealand. The bioequivalence study did not directly compare the new formulation Eltroxin with the old formulation Eltroxin. This approach of building a bridge to a formulation that Medsafe has previously approved as safe and effective is permitted under New Zealand Medicine guidelines.

The bioequivalence trial measured the levels of levothyroxine (T4) and also its physiologically active metabolite tri-iodothyronine (T3). As per standard practice, Medsafe recalculated several of the provided datasets and the results of these recalculations are summarised in table 1.

Table 1: Bioequivalence trial data comparing the newly formulated Eltroxin tablets (100µg) with a previously registered Eltroxin formulation.

Metric	Previous Formulation	New Formulation	90% Confidence Interval
Cmax value (nmolL ⁻¹) <ul style="list-style-type: none"> • TT4 • TT3 • Corrected TT4 	181.4 ± 39 1.58 ± 0.24 89.44 ± 28.33	170.5 ± 38 1.6 ± 0.22 78.9 ± 25.72	85%-92% 91%-101% 77%-89%
AUC Value (nmol.h.L ⁻¹) <ul style="list-style-type: none"> • TT4 • TT3 • Corrected TT4 	6624 ± 1393 65.64 ± 10.26 131.6 ± 45.6	6487 ± 1292 64.81 ± 8.37 124.8 ± 41.3	90%-95% 89%-98% 82%-98%
Tmax Value (hours) <ul style="list-style-type: none"> • TT4 • TT3 • Corrected TT4 	2.53 ± 1.72 16 ± 18.28 2.53 ± 1.72	3.02 ± 1.88 16.45 ± 19.08 3.02 ± 1.88	0 – 0.5 -5.79 - 7.75 0 – 0.5

In all but one instance the calculated bioequivalence values fell within the internationally accepted range of 0.8 to 1.25. The Cmax value for baseline corrected total levothyroxine (TT4) fell outside the accepted limits of 0.8 to 1.25. This result was considered acceptable given that: Cmax is not clinically important for this medicine because of its long half life (greater than 5 days), AUC is the better predictor of efficacy and safety; and the observed compliance of the remaining measurements. In addition, there is a lack of international consensus over the scientific validity of comparing baseline corrected values.

Current and future plans

On-going investigations

Medsafe will continue to investigate adverse events reported to the Centre for Adverse Reaction Monitoring (CARM) for evidence of trends and the potential cause of these reported reactions.

ESR has advised independent test results indicate the new tablets are acceptably potent and do not contain unexpected or excessive impurity content, and meet the requirements for dissolution.

Alternative levothyroxine products

Medsafe has contacted several companies regarding supply of levothyroxine products. One company (Abbott Laboratories) has now submitted an application, which is currently being evaluated. A second company

(Goldshield Healthcare NZ), whose product is currently being supplied as an unapproved medicine under Section 29 of the Medicines Act, has now expressed interest in registering its product. The company has advised it hopes to submit an application by the end of September.

It is noteworthy that neither application will include all information normally expected of an application. In particular, neither application will include a bioequivalence study comparing these products to a product previously registered in New Zealand. Instead Medsafe will be making an assessment of the clinical safety and efficacy of these products by less direct methods, such as history of use of the medicine, and bioequivalence against another medicine used internationally.

Medsafe believes that most patients experiencing adverse reactions require thyroid function monitoring and dose adjustment. Alternative brands should only be prescribed in patients with hypersensitivity (allergic) reactions and in patients exhibiting intolerance reactions to the new formulation of Eltroxin.

Patients prescribed alternative brands will need careful monitoring and dose adjustment. It is likely that the availability of greater brand choice will result in higher levels of adverse reaction reporting given overseas experience.

Appendix 1. Eltroxin Tablets: Quality Information & Testing Update as at 29 August 2008

Formulation	Old Formulation	New Formulation	Comments
Active Ingredient	Levothyroxine sodium	Levothyroxine sodium	<ul style="list-style-type: none"> • Identical active ingredient is present in both formulations • All excipients comply with international standards and are commonly used in other medicines • The formulation does not contain monosodium glutamate (MSG) or wheat based products (previous PQ's).
Excipients	Magnesium stearate	Magnesium stearate	
	Lactose monohydrate	Microcrystalline cellulose	
	Maize Starch	Pre-gelatinised Maize Starch	
	Acacia	Purified Talc	
		Silicon Dioxide	
Site of Manufacture			<ul style="list-style-type: none"> • The method of manufacture of levothyroxine has not changed (chemical synthesis) • Contrary to media reports, the product is not made using genetic engineering (recombinant technology) • The tablet is made using standard, internationally accepted manufacturing processes.
Active Ingredient	Sandoz GmbH AUSTRIA	Sandoz GmbH AUSTRIA	
Tablet	GlaxoSmithKline Inc CANADA	Glaxo Wellcome GmbH GERMANY	
Potency			<ul style="list-style-type: none"> • Medsafe initiated independent testing (by ESR) of all batches of the new formulation supplied in New Zealand and three batches of the old Eltroxin formulation • A complaint batch returned by a patient was also tested • The same batches were tested by the manufacturer GlaxoSmithKline (GSK) in parallel • All batches met specification and contain an acceptable level of levothyroxine. • Results from independent testing are comparable with results provided by the manufacturer.
Required potency standard (% of label claim)	90 – 110	90 – 110	
GSK results on re-test (%)	N/A	95.2 – 100.3	
ESR results on re-test (%)	97.7 – 100.0	91.9 – 100.0	
Purity			<ul style="list-style-type: none"> • Results from testing of the new formulation show

Levels of permitted impurities (%)	Liothyronine sodium ≤ 2.0	Liothyronine sodium ≤ 1.0 Tetrac ≤ 1.0 HDPHDB ≤ 2.5 Any other impurity ≤ 1.0 Total ≤ 5.0	<p>acceptable levels of impurities are present.</p> <ul style="list-style-type: none"> • Medsafe has requested additional testing from ESR on impurity content of the old formulation tablets • A comparison will then be made with the new formulation • Results from independent testing are comparable with results provided by the manufacturer. • A new more discriminatory test developed during reformulation of the tablets showed new impurity peaks that, on retesting of the old formulation where also shown to be present.
GSK results on re-test (%)	N/A	All results within Medsafe approved limits	
ESR results on re-test (%)	Not yet available	All results within Medsafe approved limits	
Tablet Performance			<ul style="list-style-type: none"> • Medsafe has requested additional dissolution data from GSK & ESR • Results are not expected for at least 2 weeks.
Medsafe approved standard for tablet dissolution	55% dissolution at 80 minutes	70% dissolution in 45 minutes	
GSK results on re-test	Testing not yet complete		
ESR results on re-test	Testing not yet complete		