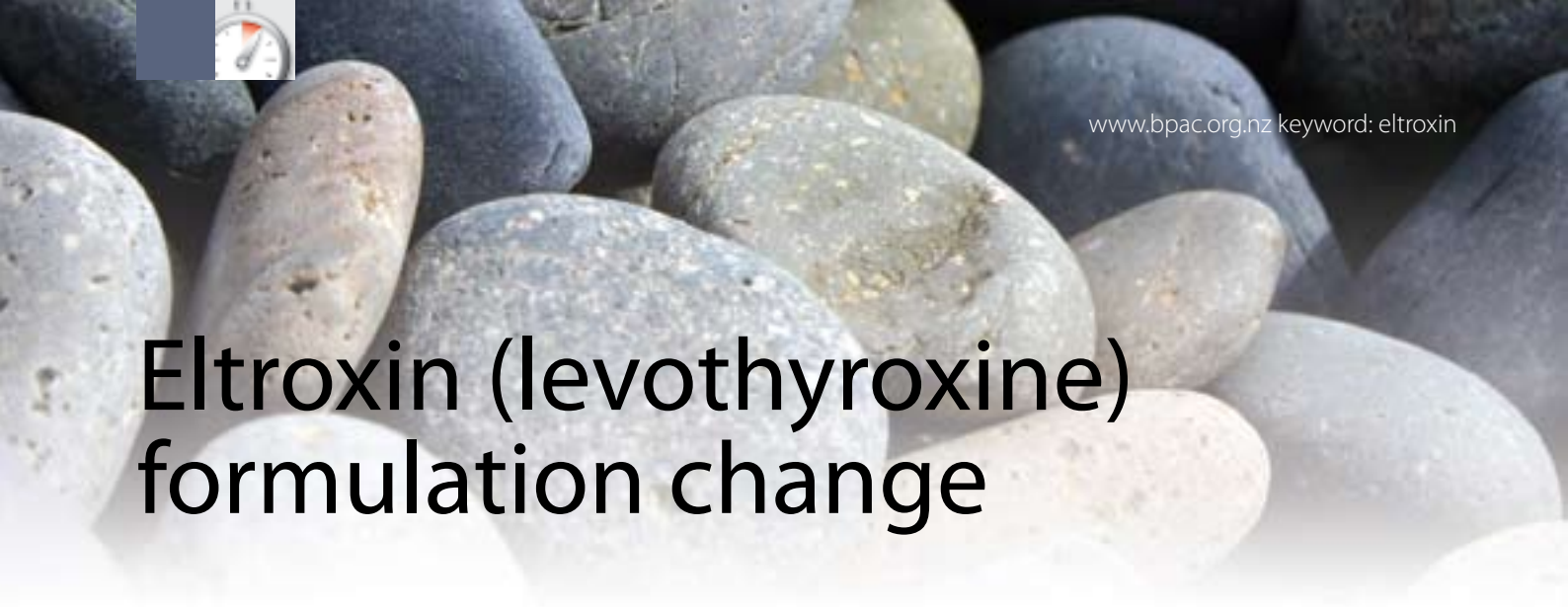

Eltroxin (levothyroxine) formulation change

New formulation of Eltroxin

Since July 2007, Glaxo Smith Kline has distributed a new formulation of Eltroxin 50 microgram and 100 microgram. The tablets have changed in size and colour and the score line has been removed. The excipients in the new formulation are also different but are commonly used in medicines.

Since then, there has been an increase in the number of adverse reaction reports involving Eltroxin, received by the Centre for Adverse Reactions Monitoring (CARM) – see side bar.

Medsafe review of Eltroxin

In response to the increase in adverse reaction reports received by CARM, Medsafe reassessed the change in formulation and confirmed that all international criteria for quality, safety, and bioequivalence were satisfactorily met.

A review of the adverse reaction reports has suggested that there is evidence of a decreased therapeutic effect in some cases. Causes of a decreased therapeutic effect may include reduced patient compliance, lack of or inappropriate blood monitoring, or quality problems with the product.

Following consultation with specialist endocrinologists, Medsafe issued advice to all healthcare professionals, emphasising the importance of thyroid function monitoring, patient compliance and how to adjust the dose of Eltroxin if necessary.

Medsafe has also initiated independent testing of the changed formulation to assess whether the presence of contaminants, or the supply of a poor quality product, could be a factor in the reactions observed. Unfortunately it will be several weeks before the results of the product testing are available.

Bioequivalence issues

Any brand or formulation change can affect the bioequivalence of a medicine. While bioequivalence is assessed using international standards before a product or formulation is approved, it is possible that up to 5% of patients may experience either an increased or decreased therapeutic effect, even when the product has been judged to be bioequivalent with the product previously available. This is why the manufacturer issued advice to all healthcare professionals, describing the change in formulation, prior to its distribution to pharmacies.

Definition of bioequivalence

Two medicines are said to be bioequivalent if the 90% confidence intervals for the ratios of the geometric means of the AUC and Cmax fall between 0.8 and 0.125 (80% and 125%). However in practice, manufacturers attempt to have this as close to 1.0 as possible.

See BPJ Special Edition March 2007 for information about bioequivalence.

Treatment of thyroid dysfunction is subject to significant inter-patient variability. Small changes in dosing of levothyroxine can affect serum thyroid hormone levels.[1]

Analysis of Eltroxin adverse reaction reports received by CARM

Approximately 70,000 patients are being prescribed Eltroxin in New Zealand.

CARM received the first report of a problem attributed to the new formulation on October 8 2007. As of August 4 2008 CARM had received 462 reports, of which 419 were received following media coverage describing patient concerns and adverse reactions in mid-June 2008. Prior to October 2007 CARM had received a total of 14 reports where thyroxine was the suspected agent.

Typical adverse reactions in the reports received by CARM include:

- Symptoms that may be attributed to thyroid dysfunction such as weight gain, lethargy, alopecia, insomnia and palpitations
- Symptoms thought unrelated to thyroid dysfunction such as eye pain, conjunctivitis, headache, visual disturbance and acute upper gastrointestinal effects
- Hypersensitivity type reactions such as angioedema, rash and facial oedema.

The onset of symptoms varies greatly in the reports. As expected, hypersensitivity reactions typically had a shorter duration of onset (days). The non-specific symptoms such as eye pain and visual disturbance also tended to have a shorter duration of onset (within the first month) whereas symptoms related to thyroid dysfunction occurred, on average, 1–2 months after conversion to the new formulation.

Details of dechallenge improvement and recurrence on rechallenge in some instances have added weight in support of a causal association with the new Eltroxin formulation.

A breakdown of reports received by CARM shows that the source of over 40% of Eltroxin adverse reaction reports were from the public, versus 29% from GPs, and 22% from pharmacists. The high proportion of reports received by the public is unusual unless a specific issue is highlighted in the media.

Possible causes of changes in therapeutic effect of Eltroxin

Slight changes in bioavailability may be an issue for patients at the upper or lower limits of the normal range.

Where TSH levels lie in the reference range, may predict how likely someone is to experience adverse effects, from a change in bioavailability.

For patients whose TSH has been adjusted to the mid-normal range, a 15% to 20% rise or fall in effective levothyroxine dose would be unlikely to result in a TSH level outside the normal range, therefore they would be unlikely to experience adverse effects.

However, a patient whose TSH level is nearer the upper or lower limits of the normal range, may be at greater risk of adverse effects with the same change, as this would be more likely to push the TSH levels outside the normal range.[2]

Patient compliance may be affected by the change in dosing instructions.

Compliance may be affected by the need to take Eltroxin tablets on an empty stomach, or the need for alternate day dosing in some patients.[1]

See Table 1 for dosing and administration recommendations from GSK.

Table 1: Dosing and administration recommendations.

Daily dose	Dosing regimen
25 microgram	One 50 microgram tablet on alternate days
50 microgram	One 50 microgram tablet daily
75 microgram	One 50 microgram tablet daily and one additional 50 microgram tablet on alternate days
100 microgram	One 100 microgram tablet daily
125 microgram	One 100 microgram tablet daily and one additional 50 microgram tablet on alternate days

Advice to prescribers

Check dosing and administration of Eltroxin[3]

1. Eltroxin tablets should be taken on an empty stomach preferably 30 minutes before breakfast.
2. Eltroxin tablets should be swallowed whole and taken with a full glass of water.
3. Doses requiring 25 microgram increments should be administered using alternate day dosing of 50 microgram tablets.

Monitor thyroid function in patients on Eltroxin[3]

Thyroid function should be monitored, particularly for patients who have noticed symptoms since changing to the new formulation.[1]

- TSH levels are the best indicator of thyroid function.
- Thyroid function tests do not have to be performed at a particular time of the day.
- Due to the long half life of levothyroxine (5–7 days) thyroid function tests should be performed no earlier than 4–6 weeks after a change in dose, or change in formulation.
- If testing is required in this first six weeks of treatment due to particular concerns about thyroid function, free T4 and free T3 levels can be monitored.

Dose adjustments in response to TSH levels should not usually exceed 50 micrograms per day. Dose adjustments in elderly people, in those with pre-existing heart disease or diabetes, should not exceed 50 micrograms on alternate days.

Report adverse reactions to Eltroxin

Adverse reactions should be reported to CARM. If possible include:

- Pre- and post- formulation change thyroid function tests (and previous dosage stability generally)
- Information on whether the patient has changed the timing of their dosage (i.e. did they take the previous formulation before or after food; and are they taking the new formulation before or after food?)
- Confirmation the patient is not halving the tablet
- When the patient was changed to the new formulation
- Whether symptoms are seemingly hyper- or hypo-thyroidism
- If any acute management was necessary

Acknowledgment:
Thank you to **Chris James**, Clinical Risk Management Team, Medsafe, for contribution to this article.

References:

1. Medsafe Press Release. Eltroxin formulation change – monitor patients and adjust dosing if necessary.
2. Green WL. New questions regarding bioequivalence of levothyroxine preparations: A clinician's response. AAPS J 2005; 7(1): E54-58.
3. Medsafe Eltroxin tablets datasheet. Available from: http://www.medsafe.govt.nz/profs/Datasheet/e/Eltroxin(new)tab.htm (Accessed 25/07/08)

Advice from Medsafe: Access to alternative levothyroxine tablets

Eltroxin is the only brand of levothyroxine tablets that has approval for distribution in New Zealand. Currently Medsafe does not have any applications for alternative brands of levothyroxine tablets from other pharmaceutical companies.

Although Medsafe is working to encourage another brand of levothyroxine to be supplied in New Zealand, the decision to market in New Zealand is not within Medsafe's control.

Any alternative brand of levothyroxine can only be supplied as an unapproved medicine. Unapproved medicines can be supplied under provisions in the Medicines Act (Sections 25 & 29) that allows an authorised prescriber to request or obtain the medicine for a specific patient under their care. Further information on the use of unapproved medicines and the obligations of the prescriber can be viewed at http://www.medsafe.govt.nz/regulatory/unapproved.asp.

The use of unapproved medicines would not usually be advocated. This is a last resort measure for people who experience significant adverse effects with Eltroxin and are unable to tolerate it. Unapproved medicines should not be routinely used in other circumstances.

Medsafe understands that Health Support Ltd is supplying an alternative brand of levothyroxine tablets using the Section 29 exemption of the Medicines Act 1981.

Medsafe has not assessed other brands or formulations of levothyroxine for quality, safety or bioequivalence. Transfer to another brand should only be considered in patients:

- With hypersensitivity or intolerance type reactions
- Exhibiting hypothyroid type symptoms that have not responded to dose adjustment.

Patients transferred to another brand of levothyroxine will require ongoing monitoring in the same way as the current GSK product.

It's time to get your patients ready for a change

Brand change notification – Losec and Omezol brands change to Dr Reddy's Omeprazole.

PHARMAC has reached an agreement with a new supplier of omeprazole. Because of this agreement only Dr Reddy's Omeprazole will be funded by PHARMAC from 1 May 2009.

This means that you have nearly 1 year to review your patient's medication.

There are a few important dates to note.

This changeover will take place over the next few months as the funding for Losec and Omezol is reduced, consequently costs may increase for Losec or Omezol, particularly if requested after these dates;

- From 1 July 2008 the cost of Omezol may go up.
- From 1 January 2009 the cost of Losec may go up.

Reference material and brand switch information about the change can be found on the PHARMAC website, www.pharmac.govt.nz.

We encourage your feedback on this brand change in a short survey accessible on **www.pharmac.govt.nz**. Follow the brand switch link found on the home page.

BrandSwitch

PHARMAC
Pharmaceutical Management Agency

New Zealand Government