Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Thyroxine sodium

Proprietary Product Name: Eltroxin, Aspen Thyrosine, Thyroxine Aspen

Sponsor: Aspen Pharma Pty Ltd

16 July 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

1. Clinical rationale

The sponsor stated:

"The aim of this development was to extend an existing drug product comprising two strengths of levothyroxine sodium tablets, namely 50 µg and 100 µg, which are currently commercialised in multiple territories worldwide, to cover a range of 11 strengths. The new range includes 25 µg, 50 µg, 75 µg, 88 µg, 100 µg, 112 µg, 125 µg, 137 µg, 150 mg, 175 µg and 200 µg tablet strengths."

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 2 clinical pharmacology studies, including 2 that provided pharmacokinetic data and 0 that provided pharmacodynamic data.
- 0 population pharmacokinetic analyses.
- 0 other efficacy/safety studies.

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

Compliance with the principles of Good Clinical Practice (GCP) was asserted for both clinical studies included in the dossier.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	ARL/11/201	
		ARL/11/196	*
	- Multi-dose	No studies	
	Bioequivalence† - Single dose	ARL/11/201	*
	- Multi-dose	No studies	
	Food effect	No studies	

PK topic	Subtopic	Study ID	*
PK in special populations	Target population § - Single dose	No studies	
	- Multi-dose		
	Hepatic impairment		
	Renal impairment		
	Neonates/infants/children/adolescents		
	Elderly		
Genetic/gender-related PK	Males vs. females	No studies	
PK interactions		No studies	
Population PK analyses	Healthy subjects	No studies	
	Target population		
	Other		

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Table 2 lists pharmacokinetic results that were excluded from consideration due to study deficiencies.

Table 2. Pharmacokinetic results excluded from consideration.

Study ID	Subtopic(s)	PK results excluded
ARL/11/201	Bioequivalence	All
ARL/11/196	General PK	All

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

3.2.1. Pharmacokinetics in healthy subjects

3.2.1.1. Bioavailability

3.2.1.1.1. Bioequivalence at different strengths

Although several strengths are proposed for registration, only the 200 µg tablet was subjected to bioequivalence testing. The evaluator could not find in the dossier any justification for this in the terms required by the relevant guideline. See next section.

3.2.1.1.2. Bioequivalence to relevant registered products

Although a bioequivalence study (ARL/11/201) was presented purporting to demonstrate bioequivalence of Eltroxin to Oroxine, the dosage used in the study was 600 µg (3 of the 200 µg tablets). Such dosage is contemplated by the relevant guideline[1] but must be justified, and the justification would depend on whether absorption kinetics are linear. The explanation given at ARL/11/201 *CSR* page 35 is:

> *"It is a challenge to determine the bioavailability of levothyroxine sodium products because levothyroxine is naturally present in minute quantities in the blood, with the total levels reaching 5.0-12.0 µg/dL and free (or unbound) levels reaching 0.8-2.7 ng/dL in a healthy adult. To assess the bioavailability of levothyroxine sodium after a single dose, several times the normal dose should be given to raise the levels of the drug significantly above baseline to allow measurement. Hence, to detect T4 above baseline levels a total dose of 600 µg was given in this study."*

This text describes the problem underlying the choice of the 600 µg dose but does not contain any justification in terms of linearity of kinetics. As the guideline makes clear, both the choice of the high dose used, and the waiver of the need to prove separately the bioequivalence of Test and Reference products at lower strengths, are dependent on such justification.

3.2.1.1.3. Influence of food

The sole bioequivalence study presented was done fasted. However, this is in compliance with the relevant guideline (EMA 2010, at page 9/27).[1]

3.2.1.1.4. Dose proportionality

This relates to linearity of absorption kinetics. No study of dose proportionality was presented or cited.

3.2.1.1.5. Dosage form proportionality

The sponsor has included in the dossier Study ARL/11/196, for which it states:

> *"The objective of this study was to assess the pharmacokinetic and dose proportionality between Test Product (A): Eltroxin (Levothyroxine Sodium) tablet 50 µg (12 x 50 µg), Test Product (B): Eltroxin (Levothyroxine Sodium) tablet 100 µg (6 x 100 µg), Test Product (C): Eltroxin (Levothyroxine Sodium) tablet 200 µg (3 x 200 µg) of Aspen Pharmacare, South Africa, following a single 600 µg administration, under fasting condition in normal, healthy, adult, human subjects, in a randomized crossover study."*

and

> *"Assessment of dose proportionality was to be done by comparing pharmacokinetic parameters of the Test Product (A): Eltroxin (Levothyroxine Sodium) tablet 50 µg, and Test Product (C): Eltroxin (Levothyroxine Sodium) tablet 200 µg with Test Product (B): Eltroxin (Levothyroxine Sodium) tablet 100 µg under fasting condition and dose proportionality would be concluded if the 90% confidence interval (CI) for geometric mean ratio between test products fall within the range of 80.00% to 125.00% for log transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Total (bound + free) T4 (for Baseline uncorrected data)."*

There seems to be considerable confusion here. Contrary to the sponsor's assertions, this was not a study of dose proportionality but of *dosage form proportionality*. The sponsor does not explain how it believes the results of this study advance the application for registration. Such a study is not mentioned in the relevant guideline.[1]

[1] European Medicines Agency (EMA). 2010. *Guideline on the Investigation of Bioequivalence.* Document CPMP/EWP/QWP/1401/98 Rev. 1/ Corr. at page 12/27

3.3. Evaluator's overall conclusions on pharmacokinetics

In relation to the single bioequivalence study submitted (no. ARL/11/201), adequate justification was not submitted for

- studying only the 200 µg strength tablet, or
- the dosage (600 µg) used in the study of the 200 µg strength tablet.

The stated objective of the other study submitted (no. ARL/11/196) appears inconsistent with the study design and the precise contribution which the sponsor believes this study makes to the present application is not clear.

4. Pharmacodynamics

No pharmacodynamics studies submitted.

5. Dosage selection for the pivotal studies

See *Summary of Pharmacokinetics* above.

6. Clinical efficacy

No efficacy studies submitted.

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

7.1.1. Pivotal efficacy studies

No studies.

7.1.2. Pivotal studies that assessed safety as a primary outcome

No studies.

7.1.3. Dose-response and non-pivotal efficacy studies

No studies.

7.1.4. Other studies evaluable for safety

7.1.4.1. Clinical pharmacology studies

Nos. ARL/11/201 and ARL/11/196.

7.1.5. Pivotal studies that assessed safety as a primary outcome

No such studies.

7.2. Patient exposure

Table 3. Exposure to Eltroxin and comparators in clinical studies.

Study type/ Indication	Controlled studies			Uncontrolled† studies	Total Eltroxin
	Eltroxin	Placebo	Oroxine	Eltroxin	
Clinical pharmacology	32	0	31	75	107
Indication 1					
Pivotal					
Other					
Subtotal Indication 1	0	0	0	0	0
TOTAL	32	0	31	75	107

† Study ARL/11/196: controlled only by treatment with other strengths of the test product, given at the same dosage (600 µg).

Table 4. Exposure to Eltroxin in clinical studies according to dose and duration.

Study type/ Indication	Proposed dose range				Proposed maximum dose			
	≥ 3 mo	≥6 mo	≥12 mo	Any dur'n	≥ 3 mo	≥ 6 mo	≥12 mo	Any dur'n
Clinical pharmacology	0	0	0	0	0	0	0	0
Indication 1								
Placebo-controlled								
Active-controlled								
Uncontrolled								
Subtotal Indication 1	0	0	0	0	0	0	0	0
TOTAL	0	0	0	0	0	0	0	0

7.3. Adverse events

7.3.1. All adverse events (irrespective of relationship to study treatment)

7.3.1.1. Pivotal studies

No pivotal studies.

7.3.1.2. Other studies

7.3.1.2.1. Study ARL/11/201

The only AEs reported were abnormal laboratory values were reported at the end of the study. Such observations had to be reported as AEs if classified as clinically significant and 6 AE reports resulted. See section 7.3.5.2.

7.3.1.2.2. Study ARL/11/196

During the study, 2 subjects [information redacted] reported vomiting and 1 subject [information redacted] reported giddiness. Other AE reports related to abnormal laboratory values reported at the end of the study. Such observations had to be reported as AEs if classified as clinically significant, and 3 AE reports resulted.

7.3.2. Treatment-related adverse events (adverse drug reactions)

7.3.2.1. Pivotal studies

No pivotal studies.

7.3.2.2. Other studies

7.3.2.2.1. Study ARL/11/201

None reported.

7.3.2.2.2. Study ARL/11/196

The 3 AEs described for this study at 7.3.1.2.2 were graded as having a "probable" relationship to study drug. The other 3 AEs (laboratory abnormalities) were graded as having a "possible" relationship to study drug.

7.3.3. Deaths and other serious adverse events

7.3.3.1. Pivotal studies

No pivotal studies.

7.3.3.2. Other studies

7.3.3.2.1. Study ARL/11/201

No such AEs reported.

7.3.3.2.2. Study ARL/11/196

No such AEs reported.

7.3.4. Discontinuation due to adverse events

7.3.4.1. Pivotal studies

No pivotal studies.

7.3.4.2. Other studies

7.3.4.2.1. Study ARL/11/201

None reported.

7.3.4.2.2. Study ARL/11/196

3 subjects [information redacted] (see above) were withdrawn from the study due to AE.

7.3.5. Laboratory tests

7.3.5.1. Pivotal studies

No pivotal studies.

7.3.5.2. Other studies

7.3.5.2.1. Study ARL/11/201

Values of laboratory tests which were outside the reference ranges at and of study and classified as clinically significant are shown in Table 5.

Table5. Study ARL/11/201. Clinically significant abnormal laboratory values at end of study. Column 1 has been redacted from the table.

Abnormal value	Reference interval	Remarks
Urinalysis showed occult blood	Negative	Repeated after 5 days, and classified NCS.
Urinalysis showed occult blood	Negative	Repeated after 5 days, and classified NCS.
Lymphocytes 59.8%	20-40%	Repeated after 5 days, and classified NCS.
ALT 76 U/L	≤ 41	Repeated after 7 days, and classified NCS.
WCC 3100	4400-11000	Subject refused to attend for review, asserting no health problems.
Basophils 19.7%	0-7%	Repeated after 9 days, and classified NCS.

7.3.5.2.2. Study ARL/11/196

Values of laboratory tests which were outside the reference ranges at and of study and classified as clinically significant are shown in Table 6.

Table 6. Study ARL/11/196. Clinically significant abnormal laboratory values at end of study. Column 1 has been redacted from the table.

Abnormal value	Reference interval	Remarks
TSH 0.01 µU/mL	0.35-5	Reassurance until resolved.
ALT 113.9 U/L	≤ 41	Reassurance until resolved.
AST 107.1 U/L	≤ 38	
TSH 0.08 µU/mL	0.35-5	Reassurance until resolved.

Perusal of the listing of laboratory measurements performed at screening shows that a high proportion of subjects appeared to be unhealthy. Of subjects 1-20 (all of whom were male), 9 had Hb below the reference range and of these 3 had MCV below the reference range. Of subjects 1-20, 10 had eosinophil % above the reference range (15.2% in the worst case). Relevant data are shown in Table 7. The sponsor should be asked to comment on the results of pre-study laboratory measurements.

Table 7. Study ARL/11/196. Values of selected laboratory parameters at screening. Column 1 (patient identification numbers) has been redacted from the table.

Hb (g/dL)[1]	MCV (fL)[2]	Eosinophils (%)[3]
12.5	66.0	6.0
12.9	69.0	1.8
13.5	83.0	1.1
12.1	73.0	2.0
12.2	80.0	4.6
13.1	83.0	3.8
12.7	82.0	5.5
12.5	66.0	6.3
13.8	96.0	5.4
13.2	83.0	6.6
13.9	85.0	5.2
14.0	78.0	8.6
12.7	88.0	1.9
15.6	96.0	5.9
14.6	87.0	5.0
13.9	84.0	15.2
14.7	94.0	2.1
14.3	89.0	3.1
12.1	89.0	2.5
12.9	84.0	6.2

[1] Reference range 13-17. [2] Reference range 80-100. [3] Reference range 0-5

7.4. Postmarketing experience

No data.

7.5. Evaluator's overall conclusions on clinical safety

In the absence of valid bioequivalence data, all the products now proposed for registration carry risks of dose error if they are used as substitutes for products currently on the market.

7.5.1. The pre-study laboratory monitoring data in Study ARL/11/196

These deserve mention. Perusal of the listing of laboratory measurements performed at screening shows that a high proportion of subjects appeared to be unhealthy. Of subjects 1-20 (all of whom were male), 9 had Hb below the reference range, and of these, 3 had MCV below the reference range. Of subjects 1-20, 10 had eosinophil % above the reference range (15.2% in the worst case). Enrolment of these subjects would appear to be quite unsatisfactory from good clinical practice and clinical trial regulation point of view given that the *Protocol* (at section 1.5) stipulated enrolment of "normal, healthy ... subjects".

In addition, it is not clear how the laboratory abnormalities observed at screening in [information redacted] (Hb and MCV below reference range) and [information redacted] (eosinophils 15.2%) came to be classified as *Not Clinically Significant*.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The proposed scored 25 µg strength fills a small unmet need. The proposed strengths 88, 112 and 137 µg offer no practical benefit beyond other proposed strengths. The additional convenience offered by the proposed 175 µg strength would be minor.

8.2. First round assessment of risks

All the proposed products carry the risk of dose error.

The proposed strengths 88, 112, 137 and 175 µg would add confusion to the range of available dosages.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of all the products which are subjects of this application, given the proposed usage, is unfavourable.

9. First round recommendation regarding authorisation

Approval of the proposed products should be refused.

10. Clinical questions

1. Could the sponsor comment on whether the pharmacokinetics of Eltroxin are linear with reference to the selection of 600 µg dose selected for the bioavailability study (ARL/11/201)? See EMA Guideline on the Investigation of Bioequivalence. CPMP/EWP/QWP/1401/98 Rev.1/Corr. P12.

2. Please comment on the clinical significance of 90% CIs for AUC_{0-t} and C_{max} being completely on the lower side of 100% in AR/11/201; that is, AUC_{0-t}: 89.1 (84.7, 93.7); C_{max}: 86.2 (82.1, 90.6).
3. Could the sponsor confirm that the 25 µg tablet is scored and can be broken equally in two?
4. Could the sponsor outline the clinical importance of the additional strengths compared to the innovator.

11. Second round evaluation of clinical data submitted in response to questions

11.1. Selected background (of relevance to the evaluation of responses)

One difference between Eltroxin and the reference product (Oroxine/Eutrosig) is that Eltroxin does not need to be refrigerated (although it should be stored below 25^{o}C).

Levothyroxine has been formulated into tablets to treat thyroid disease for more than 50 years. It is known to be difficult to manufacture; it can be sensitive to seemingly minor changes in processing; and it can be prone to instability once formulated. Historically, these known problems (and clinical reports of variations in effectiveness) have led to concerns about variations in effectiveness and stability; within and across branded products, even before the introduction of generics.

Individual patients typically have their dose of thyroxine titrated according to thyroid stimulating hormone (TSH) levels.

Eltroxin is the first generic thyroxine tablet to be submitted for registration in Australia; however, thyroxine is a well-established drug and the concept of a generic in these circumstances is not straight forward. For example, several levothyroxine products were on the market in the US and Europe before 1982 and these products were and are used interchangeably without the support of bioequivalence data required by today's regulatory standards.

Between 2000-2005 the FDA developed standards for satisfactorily establishing bioequivalence of a generic (levo)thyroxine to a reference product:

- Assays of total thyroxine in tablets
- Studies of the speed of dissolution
- Bioequivalence studies using a supra-therapeutic dose of 600mcg

There has been continuing discussion in the medical literature about the methods used in the bioequivalence studies:

- whether thyroxine is a narrow therapeutic index drug and consequently whether the acceptance limits for the 90% CI for the ratio of AUC (and C_{max}) should be 90%-111% or 80%-125%.
- whether the total thyroxine levels in bioequivalence studies should be baseline corrected (some but not all FDA documentation recommends this).

Several generic thyroxine products have gained marketing approval in the United States; however, the Endocrine Society, The American Association of Clinical Endocrinologists and the American Thyroid Association have raised continuing concerns about the bioequivalence studies. They advise that patients should avoid changing the brand of levothyroxine and if the brand is changed, TSH levels should be checked within 6 weeks.

In Europe, the Commission on Human Medicines (CHM) made the following recommendation: *"Acknowledging standard prescribing practice and that this drug product has been prescribed on a generic basis for many years, brand or named supplier prescribing is not considered necessary at this stage, but should be kept under review."* This is in line with the view of the FDA.

CHM also made the following recommendation: *"Whilst recognising the difficulties in establishing bioequivalence for levothyroxine as an endogenous substance, the CHM consider that bioequivalence studies in line with the FDA guidelines are of value in providing reassurance of bioequivalence."*

In the United Kingdom (in the 5 years to 2012), the Medicines and Healthcare Products Regulatory Agency (MHRA) advised of an increase in the number of spontaneous reports of inconsistencies in effectiveness of different makes of levothyroxine products; and between different batches of the same product.

In 2007, the British Pharmacopoeia (BP) Commission tightened the control limits for assay within the BP Monograph for Levothyroxine tablets to 90% to 105% over shelf life. These more stringent controls were intended to balance the need to allow some degradation of thyroxine during shelf-life with tighter assay limits to reduce potential variability between products and batches. In a similar move in 2007, the FDA tightened potency specifications from 90%-110% to 95%-105%.

11.2. Summary of clinical evaluation

All of the sponsor's responses are accepted, except:

- The sponsor is asked to provide baseline corrected results for the ratio of Eltroxin to the reference product for $AUC_{0\text{-}48hrs}$ and C_{max}.
- The sponsor is asked to comment on whether thyroxine is a narrow therapeutic index drug.

The regulatory decisions, at this preliminary stage and pending further advice, are around:

- Whether Eltroxin is bioequivalent and therefore interchangeable at the same dose with the reference product (Oroxine/Eutrosig).
- If Eltroxin is not considered bioequivalent to Oroxine/Eutrosig (and therefore not interchangeable at the same dose), whether the safety and efficacy of Eltroxin can be satisfactorily established via the submitted data. If this is the case, then the PIs for all three products would need to reflect the fact that Eltroxin is not interchangeable at the same dose with Oroxine/Eutrosig and patients would need to be re-titrated if they change products.

Point-by-point evaluation of the sponsor's responses to the Clinical Evaluation Report and the questions are given below.

11.2.1. Observation-1

600 µg dose for bioequivalence study

The sponsor's response is accepted.

- The EMA guideline (CPMP/EWP/QWP/1401/98 Rev.1/Corr, 2010) on bioequivalence supports the use of supra-therapeutic doses; provided that the dose is well tolerated. This allows the additional concentrations over baseline (provided by the treatment) to be reliably determined.
- The FDA Guidance for Industry on in vivo PK and bioavailability studies and in vitro dissolution testing for levothyroxine sodium tablets (2000), recommends a 600 µg dose "*to detect T4 levels above baseline levels*".

- The transcript of the Joint Public Meeting on Equivalence of Levothyroxine Sodium Products (co-sponsored by FDA, American Thyroid Association, The Endocrine Society, American Association of Clinical Endocrinologists) (2005) recommends the 600 µg dose for 2 reasons:
  - It is a multiple of the highest strength tablet (300 µg in the US)
  - It will give a strong enough signal above the background, or noise, of endogenous levels.

11.2.2. Observation 2

Dose form proportionality

The sponsor's response is accepted.

11.2.3. Observation 3

3x 200 µg tablets=600 µg dose for bioequivalence study

The sponsor's response is accepted as for Observation 1.

11.2.4. Observation 4

Adverse events

The sponsor's response is accepted.

11.2.5. Observation 5

Adverse events; withdrawals

The sponsor's response is accepted.

11.2.6. Observation 6

Unhealthy study participants, based on laboratory values (e.g., for Hb).

The sponsor's response is accepted.

11.2.7. Observation-7

Lack of adjustment for baseline T4 levels

This remains uncertain.

It is true that the FDA Guidance (2000) states that *"plasma/serum profiles and pharmacokinetic measures should be presented without adjustment of baseline levels".*

However,

- the MHRA report (2013) states: *"Whether or not correction for baseline levels should be employed in these studies is still being debated."*
- the FDA transcript (2005) (p59, [information redacted], FDA) states: *"And before performing the bioequivalence statistics, the baseline is subtracted from the AUC, and as I mentioned earlier, this is required of all the applicants. And for levothyroxine, the baseline actually makes a fairly high contribution to the plasma concentration profile. So a good chunk of the AUC, the non-corrected AUC, is being subtracted. And this really provides an extra level of assurance that the two products are bioequivalent, because this is a very conservative approach. In other words, it can be easier for two products that are not bioequivalent to pass without baseline correction, whereas if two products are not bioequivalent, there's a much higher likelihood that this is going to be detected with the baseline correction."*
- The EMA Guideline on bioequivalence states: *"If the substance being studied is endogenous, the calculation of pharmacokinetic parameters should be performed using baseline correction so that the calculated pharmacokinetic parameters refer to the additional concentrations provided by the treatment."*

The sponsor is asked to provide a comparison between the product they are proposing for registration and the reference product, for AUC_{0-48} and C_{max}, adjusted for baseline values; with 90% CIs. (The method of baseline adjustment should be reported.)

11.2.8. Observation 8

Omitted data for subjects [information redacted]

Sponsor's response is accepted.

11.2.9. Query 16

Linear pharmacokinetics

It is accepted that dose linearity studies have not been conducted with actual therapeutic strengths because of the difficulties associated with measuring the contribution of exogenous thyroxine.

11.2.10. Query 17

90% CI for AUC and C_{max} are completely on the lower side of 100%: AUC: 89% (85%, 94%); C_{max}: 86% (82%, 91%)

It is accepted that this meets the criterion for bioequivalence if thyroxine is not considered a narrow therapeutic index drug (see below).

Is thyroxine a narrow therapeutic index drug?

The sponsor is invited to comment on this issue.

Some experts consider that thyroxine is a narrow therapeutic index drug (for example MHRA report). Examples of subsets of patients for whom differences in bioavailability could have important clinical implications include:

- Patients with a previous history of thyroid cancer. Low levels of T4 could lead to an unexpected increase in TSH and recurrence of thyroid cancer
- Young patients with congenital thyroid disease. Low levels could lead to suboptimal growth and brain development.
- Pregnant women. Low levels could lead to harm to their babies.
- Patients with co-existing cardiac disease. High levels could lead to atrial fibrillation and other arrhythmias.
- Elderly women. There is suggestive evidence that, over long periods, high levels can cause or aggravate osteoporosis.

For narrow therapeutic index drugs, the acceptance interval for AUC is usually tightened to 90% to 111%.

The 2010 EMA Guideline on bioequivalence states: *"It is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTID based on clinical considerations."*

The 2013 MHRA report states:

- There is no agreed European definition of narrow therapeutic index drugs (as above)
- It refers to the FDA definition:
  - <2-fold difference between minimum toxic and minimum effective concentrations in blood, or;
  - safe and effective use requires careful titration and patient monitoring.

It concludes that (p8): *"Therefore, although levothyroxine does not meet the criteria for being a narrow therapeutic index drug, there are strong indications that small changes in the delivered dose of levothyroxine, should they persist over long term treatment, could have significant clinical consequences."*

The 2000 FDA Guidance for Industry and the 2005 transcript of the Joint Public Meeting on Equivalence of Levothyroxine Sodium Products, refer to an acceptance interval of 80% to 125%.

12. References

Blakesley VA. 2005. Current methodology to assess bioequivalence of levothyroxine sodium products is inadequate. *The AAPS Journal* 7(1): Article 5 (http://www.aapsj.org).

Bolton S. 2005. Bioequivalence studies for levothyroxine. *The AAPS Journal* 7(1): Article 6 <http://www.aapsj.org>.

European Medicines Agency (EMA). 2010. *Guideline on the Investigation of Bioequivalence.* Document CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.

FDA. 2000. *Guidance for Industry. Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing.*

Therapeutic Goods Administration (TGA). 2004. *Australian Regulatory Guidelines on Prescription Medicines.* Appendix 15: Biopharmaceutic studies.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au