



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Thyroxine Sodium

Proprietary Product Name: Eltroxin, Aspen
Thyroxine, Thyroxine Aspen

Sponsor: Aspen Pharma Pty Ltd

June 2014

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- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of commonly used abbreviations

Abbreviation	Meaning
CI	Confidence interval
C _{max}	Peak plasma drug concentration
AUC	Area under the plasma concentration time curve
PI	Product information
PK	Pharmacokinetics
T3	Tri-iodothyronine
T4	Thyroxine
TT4	Total thyroxine

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New generic and new strength
<i>Decision:</i>	Approved
<i>Date of decision:</i>	9 May 2014
<i>Active ingredient:</i>	Thyroxine Sodium
<i>Product names:</i>	Eltroxin, Aspen Thyroxine, Thyroxine Aspen
<i>Sponsor's name and address:</i>	Aspen Pharma Pty Ltd 34-36 Chandos St St Leonards NSW 2065
<i>Dose form:</i>	Tablets
<i>Strengths:</i>	25, 50, 75, 88, 100, 112, 125, 137, 150, 175 and 200 µg
<i>Container:</i>	Plastic Bottles
<i>Pack size:</i>	200's
<i>Approved therapeutic use:</i>	<i>Eltroxin is indicated for the management of demonstrated thyroid hormone deficiency.</i> <i>Eltroxin is also used to suppress thyrotropin (TSH) for the management of TSH-responsive tumours of the thyroid.</i>
<i>Route of administration:</i>	Oral (PO)
<i>Dosage:</i>	The dose is individualised on the basis of clinical response: initial doses are 50 to 100 µg/day; the usual maintenance dose is 100 to 150 µg/day; and the maximum dose is not specified.
<i>ARTG numbers:</i>	206944, 206946, 206950, 206954, 206958, 206960, 206961, 206963, 206966, 206967, 206974

Product background

This AusPAR describes the application by the sponsor, Aspen Pharma Pty Ltd, to register a generic version of an already in Australia marketed product Oroxine/Eutroxsig (thyroxine sodium). Aspen is also the sponsor of Oroxine/Eutroxsig.

The sponsor has proposed the following indication for Eltroxin (Aspen Thyroxine; Thyroxine Aspen):

- management of demonstrated thyroid hormone deficiency
- suppression of thyrotropin (TSH) for the management of TSH-responsive tumours of the thyroid
- management of thyroiditis such as Hashimoto's disease

Thyroxine is an essential medicine for the treatment of hypothyroidism and is widely prescribed. In the US, the leading brand of thyroxine is the third most widely prescribed pharmaceutical product.

It 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. Historically, these known problems have led to concerns about variations in effectiveness and stability; within and across branded products, even before the introduction of generics. A recent Medicines and Healthcare Products Regulatory Agency (MHRA) report [2013] noted the problem of formulation-related variability, where differences in not active ingredients (excipients) in different tablet products can cause changes in dissolution, bioavailability, and therapeutic response.

Eltroxin is the first generic thyroxine tablet to be submitted for registration in Australia. This is unusual; in most other similar countries there are more than one thyroxine formulations on the market. Aspen Pharma Pty Ltd has proposed the same indication for Eltroxin as for the registered products.

Aspen Pharma Pty Ltd proposes to register eleven (11) strengths of tablets containing 25 mg, 50 mg, 75 mg, 88 mg, 100 mg, 112 mg, 125 mg, 137 mg, 150 mg, 175 mg or 200 mg of thyroxine sodium. Currently there are four strengths of thyroxine sodium tablets registered in Australia: 50 mg, 75 mg, 100 mg and 200 mg tablets. (registered as Oroxine and Eutroxig). The proposed products are therefore generic products of the registered strengths with seven (7) additional strengths in order to give a more accurate control of the dose.

Oroxine/Eutroxig requires refrigeration whereas Eltroxin does not.

Regulatory status

Oroxine has been registered in Australia since 2006.

The following is a summary of the current overseas regulatory status for this product:

New Zealand

A similar product is approved and marketed in New Zealand. The current formulation of the product was approved in November 2006 and is available in 50 and 100 µg strength tablets only. The formulation of the 50 µg tablet is the same as the product proposed for registration in Australia but the formulation of the 100 µg tablet differs in the quantity of the excipients.

Canada

A product containing the same active ingredient is approved and marketed in Canada but the formulation of the product is different.

EU

Decentralised procedure

- A similar application was submitted via the Decentralised Procedure on 18 July 2012 (strengths: 25, 50, 75, 88, 100, 112, 125, 137, 175 and 200µg).
- The Reference Member State (RMS) is the Netherlands.
- Concerned Member States (CMS) are: Sweden, Ireland, Germany, Belgium, Spain, Luxembourg, France, Italy, Norway, Finland and Denmark.

US

- A similar application has been submitted on 16 March 2012 (strengths: 25, 50, 75, 88, 100, 112, 125, 137, 175, 200 and 300µg).
- Current status of submission: Received the assessment conducted by the Office of Generic Drugs (OGD) Division of Bioequivalence II (DBII) on the dissolution testing portion of the submission. Aspen is in the process of preparing a response to a deficiency letter.
- Also received a query on the proposed product name and Aspen are in process of compiling a response.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

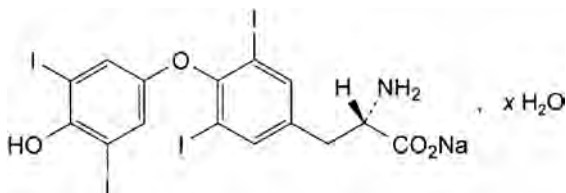
II. Quality findings**Introduction**

The proposed products are a different formulation to the registered tablets. They are also manufactured by a different method of manufacture: direct compression versus wet granulation. These changes were made to increase the stability of the tablets but a consequence of this is that the extent and rate of dissolution of the proposed tablets are less than those of the registered tablets.

There are British Pharmacopeia (BP), European Pharmacopeia (EP) and US Pharmacopeia (USP) monographs for the drug substance and BP and USP monographs for the tablets.¹

Drug substance (active ingredient)

Thyroxine is a naturally occurring thyroid hormone. This product is formulated with the sodium salt and the form of the sodium salt used is the pentahydrate.

Figure 1. Chemical structure of thyroxine sodium

Sodium (2S)-2-amino-3-[4-(4-hydroxy-3,5-diodophenoxy)-3,5-diodophenyl]propanoate pentahydrate. $C_{15}H_{10}I_4NNaO_4 \cdot xH_2O$ with $x = 5$; molecular mass = 888.91, CAS number 25416-65-3
Anhydrous material: $C_{15}H_{10}I_4NNaO_4$ molecular mass = 798.85; CAS number 55-03-8

The material is manufactured by chemical synthesis and is a single enantiomer. It is a white or slightly brownish-yellow, slightly hygroscopic, crystalline powder. It is very slightly soluble in water, slightly soluble in ethanol but dissolves in dilute alkali solutions.

¹ Note that although the Australian Approved Name (AAN) for the drug substance is Thyroxine Sodium, the rest of the world refers to the drug substance as Levothyroxine Sodium. The monographs are therefore titled Levothyroxine Sodium (BP, EP, USP), Levothyroxine Tablets (BP) and Levothyroxine Sodium Tablets (USP).

The material is manufactured to meet the BP/EP monograph for Levothyroxine Sodium. The related substances are also controlled as per the BP/EP monograph.

Drug product

The proposed products were developed to be generics of the registered tablets but to have a number of additional strengths to allow for accurate dosing. They were also reformulated (as mentioned in the introduction) to give a more stable product than the registered tablets.

The different strengths of the proposed tablets are all the same mass, with the (small) differences in the masses of the drug substance being compensated for with differences in the amounts of microcrystalline cellulose added. They are also the same colour (white), but are distinguished by their markings (embossing) and different coloured labelling. The registered products are all direct scales.

As mentioned in the introduction, the change in formulation and method of manufacture has led to a lower dissolution compared to the registered products. This is seen across the physiological pH range.

In relation to the proposed dissolution test method, this is not considered acceptable as it is not sufficiently discriminative.

The method is based on Dissolution Tests 1-3 in the USP monograph for Levothyroxine Sodium Tablets. This is also the dissolution method of the current tablets.

More recently, the BP monograph for Levothyroxine Tablets has been updated.

It is clear that the presence of sodium lauryl sulfate (SLS) was required to give a reasonable dissolution profile, and it was accepted that the BP method (without SLS) was unsuitable for routine quality control.

The proposed method is similar to the USP dissolution method. Data comparing the USP dissolution method and the proposed dissolution method indicates that the USP dissolution method will be more discriminative and be able to ensure a consistent manufacturing process and that the dissolution of the tablets does not slow on storage.

The proposed finished product specifications include appropriate parameters and the following should be noted.

There are acceptable limits for assay.

There are acceptable limits for individual impurities.

There is a suitable limit for total impurities.

There is a suitable limit for water content.

There is a suitable limit for dissolution. This limit is based on the results of the batch of tablets used in bioequivalence study ARL/11/201. The limit is tighter than that in USP Dissolution Test 1 but not as tight as that in USP Dissolution Test 3. Note that the limit must be used with the USP dissolution method rather than the proposed dissolution method, see above.

There are also limits for hardness, but these are probably not acceptable as tablets with higher hardness will not pass the dissolution limit using the USP dissolution method. Note the batch used in bioequivalence study ARL/11/201 had a hardness of 31 N.

The 25 mg tablet is scored with a break-line and uniformity of content and dissolution data were provided to demonstrate that they break in an acceptable manner and this does not significantly affect the dissolution rate.

Stability data were generated under accelerated and long-term conditions on batches packaged in the proposed container closure system (which includes a child-resistant closure). This would support a shelf life of 2 years when stored below 25°C with the condition protect from light. The tablets are more stable than the registered products and this is thought to be due to the fact that the levothyroxine sodium remains as the pentahydrate in these tablets as they were manufactured by direct compression with no drying step. A drying step would be necessary to remove excess granulating fluid when the method of manufacture is wet granulation.

The proposed carton and bottle labels and PIs are acceptable from PCS perspective.

Biopharmaceutics

The submission included a bioequivalence study comparing the proposed 200 mg tablets to the registered 200 mg tablets (Study ARL/11/201) and a study comparing the bioavailability of the proposed 50 mg, 100 mg and 200 mg tablets all at the same dose (ARL/11/196). This approach is specified in a US FDA Guidance on Levothyroxine Sodium Tablets.

Thyroxine (T4) is extensively protein bound. It is metabolised by de iodination first to inactive tri-iodothyronine (T3) and then to further inactive species with less iodine. There is some enterohepatic recycling of T3 back to T4.

The bioanalytical test method used in the two studies was the same and was based on chemiluminescence. The method was appropriately validated and can quantify free T4, total (Bound + free) T4, free T3 and total (Bound + free) T3.

Study ARL/11/201

This study compared the test and reference products at a dose of 600 µg (3 x 200 µg tablets).

Thyroxine is endogenous and data before and after a baseline correction was provided. However in accordance with the US FDA Guidance, bioequivalence was assessed on the non-baseline-corrected results for total (bound + free) T4.

The point estimates and 90% confidence intervals for uncorrected total (bound + free) T4 are given directly below.

Table 1. Geometric means and 90% confidence interval of baseline uncorrected total (free+unbound) T4 (n=31).

Parameters	*Geometric mean		% Ratio A/B	90 % Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)		Lower Limit	Upper Limit
AUC _{0-t}	442.85	497.06	89.0954	84.7357	93.6795
C _{max}	11.80	13.69	86.2188	82.0626	90.5854

*Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.

It can be seen from the above point estimates that the test product has a lower bioavailability than the reference product (11% lower). Statistically this is confirmed in that if wider confidence intervals were calculated they would cross the lower limit of 80.00% before the upper end reached 1. This lower bioavailability is most likely a direct result of the lower extent and rate of dissolution of the test product (see above). There is doubt as to whether the usual limits of 80.00 to 125.00% for the 90% confidence intervals should apply to this product but this is a clinical issue.

Study ARL/11/196

This study compared three strengths of the test products at a dose of 600 µg (12 x 50 µg tablets, 6 x 100 µg tablets and 3 x 200 µg tablets).

As for study ARL/11/201, the results for total (bound + free) T4, total (bound + free) T3, free T4 and free T3, were provided for both before and after a baseline correction. However in accordance with the US FDA Guidance, dose proportionality was assessed on the non-baseline-corrected results for total (bound + free) T4.

The point estimates and 90% confidence intervals for uncorrected total (bound + free) T4 are given directly below.

Table 2. Geometric means and 90% confidence interval of baseline uncorrected total (free+unbound) T4 (n=67).

Comparison of Test A with Test B for Total (bound+free)T4 (Uncorrected):

Parameters	*Geometric Mean		% Ratio	90 % Confidence Interval for Log-transformed data	
	Test (A)	Test (B)		A/B	Lower Limit
AUC ₀₋₄	424.496	404.556	104.9287	101.5467	108.4233
C _{max}	11.816	10.972	107.6953	104.6300	110.8505

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.

Comparison of Test C with Test B for Total (bound+free)T4 (Uncorrected):

Parameters	*Geometric Mean		% Ratio	90 % Confidence Interval for Log-transformed data	
	Test (C)	Test (B)		C/B	Lower Limit
AUC ₀₋₄	417.882	404.556	103.2940	99.9647	106.7342
C _{max}	11.471	10.972	104.5559	101.5799	107.6191

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.

The point estimates of the three strengths are close to unity and the 90% confidence intervals are well within 80.00 to 125.00 and in fact within 90.00-111.11%. It can therefore be concluded that the different strengths give rise to the same bioavailability.

Justification for not providing bioequivalence data on all strengths of the proposed tablets

The sponsor provided such a justification. This was acceptable from a pharmaceutical chemistry perspective based on comparative dissolution profiles for all the strengths. The clinical aspects were not evaluated here.

Advisory committee considerations

The advice of TGA's Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) was not requested.

Quality summary and conclusions

Product registration is not recommended from a chemistry and quality perspective.

The proposed tablets are manufactured in a manner which leads to lower dissolution relative to the Australian innovator. Therefore it is important to have a discriminative dissolution test method and associated limit. The sponsor has shown that the method of USP Dissolution Test 1-3 is suitable. The dissolution method being proposed does not appear to discriminate between products that may not be bioequivalent based on their dissolution profiles. This reflects a need to re-examine other aspects of the product development and product specification (that is, tablet hardness) that may affect the dissolution profile of the product.

Furthermore, the proposed products have lower bioavailability (11% lower) compared to the Australian innovator product. Therefore if the 90% confidence interval of 80.00 to

125.00 is not acceptable for this product and the product cannot be considered a generic version of the registered Oroxine/Eutroxig tablets. Registration is not recommended unless there are compelling clinical reasons for its approval.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

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."

Contents of the clinical dossier

The submission contained the following clinical information:

- 2 clinical pharmacology studies, including 2 that provided pharmacokinetic data. There were no studies provided pharmacodynamic data.
- 0 population pharmacokinetic analyses.
- 0 other efficacy/safety studies.

Paediatric data

The submission did not include paediatric data.

Good clinical practice (GCP)

Compliance with the principles of GCP was asserted for both clinical studies included in the dossier.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 3. 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 in special populations	Target population § Single dose	No studies	
	- Multi-dose		
	Hepatic impairment		
	Renal impairment		
	Neonates/infants/children/a dolescents		
	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 4 lists pharmacokinetic results that were excluded from consideration due to study deficiencies.

Table 4. Pharmacokinetic results excluded from consideration.

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

Evaluator's 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.

Pharmacodynamics

No pharmacodynamics studies were submitted.

Dosage selection for the pivotal studies

See *Summary of Pharmacokinetics* above.

Efficacy

No pivotal efficacy studies were submitted.²

Safety

The following studies provided evaluable safety data:

Pivotal efficacy studies

No studies.

Pivotal studies that assessed safety as a primary outcome

No studies.

Dose-response and non-pivotal efficacy studies

No studies.

Other studies evaluable for safety

Clinical pharmacology studies

Studies ARL/11/201 and ARL/11/196.

Pivotal studies that assessed safety as a primary outcome

No pivotal safety studies were submitted.

² Two PK studies were submitted ARL/11/196: intended to assess dose proportionality for the 50 µg, 100 µg and 200 µg Eltroxin tablets and ARL/11/201: intended to assess bioequivalence between Eltroxin and the reference registered product, Oroxine

Patient exposure**Table 5. 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 6. Exposure to Eltroxin in clinical studies according to dose and duration.

Study type/ Indication	Proposed dose range				Proposed maximum dose			
	≥ 3	≥ 6	≥ 12	Any	≥ 3	≥ 6	≥ 12	Any
	mo	mo	mo	dur'n	mo	mo	mo	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

Postmarketing data

No data were submitted.

Evaluator's conclusions on 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.

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 Hb and MCV below reference range and eosinophils 15.2% came to be classified as *Not Clinically Significant*.

First round benefit-risk assessment**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.

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.

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.

First round recommendation regarding authorisation

Approval of the proposed products should be refused.

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 product.

Second round evaluation of clinical data submitted in response to questions

Background of relevance to the evaluation of the sponsor's responses

One difference between Eltroxin and the reference product (Oroxine/Eutroxig) is that Eltroxin does not need to be refrigerated (although it should be stored below 25°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 600 µg

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% to 111% or 80% to 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%.

Summary of clinical evaluation

All of the sponsor’s responses are accepted, except the sponsor was asked to:

- provide baseline corrected results for the ratio of Eltroxin to the reference product for $AUC_{0-48hrs}$ and C_{max} .
- 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/Eutroxig).
- if Eltroxin is not considered bioequivalent to Oroxine/Eutroxig (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/Eutroxig and patients would need to be re-titrated if they change products.

Point-by-point evaluation of the sponsor’s responses to the First Round clinical evaluation report and the questions are given below.

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.

Observation 2

Dose form proportionality

The sponsor's response is accepted.

Observation 3

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

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

Observation 4

Adverse events

The sponsor's response is accepted.

Observation 5

Adverse events; withdrawals

The sponsor's response is accepted.

Observation 6

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

The sponsor's response is accepted.

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) 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.)

Observation 8

Omitted data for eight subjects

Sponsor's response is accepted.

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.

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.³ 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;

³ 2013 MHRA report and 2005 FDA transcript

- 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%.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan version 1, data lock point 12 October 2012) with Australian Specific Annex (version 0.1, dated 11 March 2013) which was reviewed by the TGA’s Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 7.

Subject to the evaluation of the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

Table 7. Summary of ongoing safety concerns

Important Identified Risks	Cardiotoxicity, Treatment imbalance leading to hypothyroidism and hyperthyroidism Fracture linked to hyperthyroidism Adrenal crisis Hyperglycaemia in diabetic patients Drug interactions
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‘Drug abuse in weight loss’ has been listed as an identified safety risk in the pharmacovigilance and risk minimisation plan in the proposed RMP. The sponsor should include this risk in the ‘Summary of Safety Concerns’.

Pharmacovigilance plan

The sponsor has proposed routine pharmacovigilance for all important identified risks. In addition, a specific Adverse Drug Reaction (ADR) Form is proposed for Cardiotoxicity and Treatment imbalance leading to hypothyroidism and hyperthyroidism *in order to gather more accurate information on patient status, change of dosage, change of brand, latest hormonal levels, new concomitant drugs*. The sponsor should provide a sample of such form to the TGA for evaluation.

The sponsor justification for their proposal of routine pharmacovigilance activities for all safety risks based on the well understood safety profile of levothyroxine was considered acceptable.

Risk minimisation activities

The sponsor proposes routine and additional risk minimisation activities (development and distribution of educational materials to Consumers and Healthcare Professionals prepared in accordance with Medicines Australia Code of Conduct Guidelines) for all the ongoing safety concerns.

The sponsor's evaluation of the need for risk minimisation activities was considered to be satisfactory.

Reconciliation of issues outlined in the RMP report

Table 8 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 8. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>'Drug abuse in weight loss' has been listed as an identified safety risk in the pharmacovigilance and risk minimisation plan in the proposed RMP. The sponsor should include this risk in the 'Summary of Safety Concerns'.</p>	<p><i>RMP has been updated regarding 'Drug abuse in weight loss'. Based on estimated patient exposure of approximately 224 million patient-years for the 100 microgram daily dose and 148 million patient-years for the 150 microgram daily dose for the 50-year post-authorisation period, and the potential for drug abuse with levothyroxine is considered to be low. Hence all reference to drug abuse in weight loss has been removed from the RMP.</i></p>	<p>The sponsor's response was considered to be acceptable.</p>
<p>The sponsor proposes a specific adverse reaction form for the identified risks 'in order to gather more accurate information on patient status, change of dosage, change of brand, latest hormonal levels, new concomitant drugs', the sponsor should provide a sample of such form to the TGA for evaluation.</p>	<p><i>The following 2 ICSR Follow-Up Questionnaires had been agreed and were submitted to the TGA.</i></p> <p><i>Cardiac Adverse Events</i></p> <p><i>Potential Hypo- or Hyper – Thyroidism or Treatment Imbalance.</i></p>	<p>The sponsor's response was considered to be acceptable.</p>
<p>The evaluator agrees that the introduction of more strengths will help minimise the potential for some medication errors as the sponsor has stated. However, eleven different</p>	<p><i>The risk of medication errors can be reduced by packaging with the judicious use of different colours to distinguish different strengths on the carton pack and inclusion of unique embossing on each and</i></p>	<p>The sponsor's response was considered to be acceptable.</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>strengths are likely to become a potential for medication errors especially during dispensing and administration of the product. The sponsor should provide justification as to how the proposed risk minimisation activities can help avoid confusion and potential medication errors caused by the introduction of seven more strengths.</p>	<p><i>every strength of the tablet.</i></p> <p><i>To prevent potential medication errors that may occur due to the availability of a wide range of levothyroxine sodium strengths in the market, Aspen has taken due care</i></p> <p><i>In artwork by customising a particular colour to the carton against each strength</i></p> <p><i>Each tablet is embossed with its relevant strength on one side (see attached artwork).</i></p> <p><i>This is clearly stated in the product information (SPC & PIL)</i></p> <p><i>Thus, different tablet strengths are distinguishable at a level sufficient to avoid mistakes between the different strengths by the patient and health-care professional.</i></p> <p><i>With regard to the analysis of the identified risks with any levothyroxine product, the creation of a website answers all the objectives above. The use of all new channels of communication is recommended, due to their relevance to the public and Health care Professionals (HCPs) for easy access to information.</i></p> <p><i>Risk communication will be focused on treatment imbalance, which is encompassing almost all other risks, and will describe the risks factors and the populations at risk. Risk communication will be performed through a dedicated website, with two discrete sections: one for healthcare professionals and the other for patients. In both sections, a quiz with multiple answers will evaluate the understanding of the reader.</i></p> <p><i>Risk communication will be</i></p>	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p><i>performed through a dedicated website, with two discrete sections: one for healthcare professionals and the other for patients. In both sections, a quiz with multiple answers will evaluate the understanding of the reader.</i></p> <p><i>The effectiveness of the website as a risk minimization measure will be assessed via the two quizzes, and website traffic metrics. Annual analysis will be performed.</i></p> <p><i>Training will be provided to relevant personnel in Aspen affiliates and partners to make them aware of the website as a risk minimisation tool, to ensure it is used correctly and to remind them of the correct indications for use of levothyroxine.</i></p>	
<p>It is recommended that the sponsor provides the educational materials to the TGA prior to supply.</p>	<p><i>Aspen agree that all the necessary educational/ training materials will be provided to TGA prior to distribution.</i></p>	<p>The sponsor's response was considered to be acceptable.</p>

Summary of recommendations

It was considered that the sponsor's response to the TGA has adequately addressed all of the issues identified in the First Round RMP evaluation report. Outstanding issues are detailed below.

Outstanding issues

Issues in relation to the RMP

Refer to 'Comments on the safety specification of the RMP' below.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Comments on the safety specification of the RMP

Clinical evaluation report

No comment was made on the safety specification of the RMP in Second Round Clinical Evaluation report. However, the clinical evaluator raised the issues of bioequivalence among different levothyroxine products and whether thyroxine should be considered as a drug of narrow therapeutic index. The clinical evaluator states:

'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.'*

The OPR evaluator supports the comments and concerns raised in the clinical evaluation report. There is a risk of patients responding differently when switching products. The consequence can be serious especially in special patient groups mentioned above. Therefore, this risk should not be ignored. It is recommended that '*change in clinical response when switching brands*' be added as an 'important potential risk' in the Australian-specific Annex.

Suggested wording for conditions of registration

RMP

Implement RMP (version 1, data lock point 12 October 2012) with Australian Specific Annex (version 0.1, dated 11 March 2013), to be revised to the satisfaction of the TGA, must be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Consideration of the strengths proposed

Taking into account the doses which can be achieved by halving a scored tablet, the available doses $\leq 200 \mu\text{g}$ using either 2 whole, or ≤ 1 whole and/or ≤ 1 half of currently registered tablets are: 25, 50, 37.5, 75, 87.5, 100, 112.5, 125, 137.5, 150, 175 and $200 \mu\text{g}$. Thus (apart from doses comprising half a $25 \mu\text{g}$ tablet plus another tablet, or combinations of generic with another product) the sponsor is proposing to make available the following additional dose options: 12.5, 88, 112 and $137 \mu\text{g}$.

The Delegate thought the possibility of achieving doses of 87.5, 112.5 and $137.5 \mu\text{g}$ is a quirk of the combinatorial possibilities, and doubted the clinical need for any such dose. Besides, if the need did arise for such fine adjustment of dosage (say, from 75 to $87.5 \mu\text{g}$, from 100 or 125 to $112.5 \mu\text{g}$, or from 125 to 112.5 or $137.5 \mu\text{g}$), the generic could not be regarded as equivalent to the market leader over such a small change. An additional objection to the proposed 88, 112 and $137 \mu\text{g}$ strengths is that they would add to the market 3 strengths formally but trivially different from doses (87.5, 112.5 and $137.5 \mu\text{g}$) which are already achievable with marketed products.

The fact that a $200 \mu\text{g}$ tablet has been approved implies approval of dosage to at least that level and in any case this range is well known in clinical practice. The Oroxine PI envisages doses as low as $12.5 \mu\text{g}$ so the addition to the market of a scored $25 \mu\text{g}$ tablet is desirable. Also, doses of 125 and $150 \mu\text{g}$, not uncommonly used in clinical practice, currently require the use of tablet fragments and the Delegate had no objection in principle to the introduction of these tablet strengths for convenience.

This leaves for consideration the proposed 175 µg strength. This dose may be occasionally used in clinical practice but approval of a generic tablet of this strength would be subject to the objection described in the sentence commencing "Besides", two paragraphs above.

Bioequivalence

Establishing the bioequivalence of different thyroxine formulations is not straight forward. Some expert clinical groups (such as American Association of Clinical Endocrinologists, The Endocrine Society) recommend brand prescribing of thyroxine and there has been continuing discussion in the medical literature, over more than 25 years, about the methods used to establish bioequivalence. The two main methodological issues are 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% to 111% or 80% to 125%.
- the total thyroxine levels in bioequivalence studies should be baseline corrected (some but not all FDA documentation recommends this).

These two issues are discussed below:

Is thyroxine a narrow therapeutic index (NTI) drug?

The therapeutic index (or therapeutic ratio) is a comparison of the amount of a drug that causes the therapeutic effect with the amount that causes adverse reactions. Narrow therapeutic index drugs are drugs with small differences between therapeutic and toxic doses.

Some experts consider that thyroxine is a narrow therapeutic index drug³; at least for some subsets of patients. Examples of subsets of patients for whom there is a relatively narrow window for dosing and for whom differences in bioavailability across different brands of thyroxine 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 on thyroxine 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, and

- safe and effective use requires careful titration and patient monitoring.

It concludes that: *“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%. The acceptance interval of 80% to 125% (rather than 90% to 111%) implies that the FDA does not consider (levo)thyroxine a narrow therapeutic index drug.

Acute toxicity is a key characteristic of NTI drugs in practice. This does not typically occur with thyroxine in the short term; also thyroxine has a long half-life. Therefore, thyroxine is not a typical NTI drug. Nevertheless, small changes in the dose of thyroxine, should they persist over long term treatment, could have significant clinical consequences; especially for certain subsets of patients (see above).

In short, there is no consistent or coherent guidance in the literature or among regulatory agencies as to whether thyroxine is a narrow therapeutic index drug and whether the 90% acceptance interval should be 80% to 125% or 90% to 111%.

Should total thyroxine levels in bioequivalence studies be baseline corrected?

The FDA Guidance on levothyroxine (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) 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.”*

An additional consideration is that the FDA guideline recommends that bioequivalence studies are done in healthy volunteers using a supra-therapeutic dose of 600 µg. This is meant to overcome the potential problems of background endogenous interference; however, not all experts agree that use of a supra-therapeutic dose (as done in Study ARL/11/201 in this current submission) avoids the need for baseline correction; and some FDA documentation states that it does not (see second dot point immediately above).

Background interference from endogenous thyroxine could be overcome by recruitment of patients deficient in endogenous thyroxine; however, this is usually not practical or ethical. Also, heterogeneity in the extent of the deficiency means that the patients recruited are less well defined and the study less well controlled than a study among

healthy volunteers. A bioequivalence study of patients already on replacement therapy would be complicated by variable baseline control.

TSH has been proposed as an alternative biochemical marker in bioequivalence studies of thyroxine. However, variability of TSH, as a secondary effect is high (co variance (CV) approximately 200%)⁴ and use of TSH in bioequivalence studies is not considered feasible.

In short, the current standard for bioequivalence studies of thyroxine is to give supra-therapeutic doses (600 µg) to healthy volunteers. There is no consistent or coherent guidance in the literature or among regulatory agencies as to whether thyroxine levels should be baseline corrected, regardless of whether a supra-therapeutic dose is used.

MHRA 2013 report: Levothyroxine tablet products: A review of clinical and quality considerations

MHRA published a report in 2013⁴ following persistent concerns from healthcare professionals and patient organisations as to whether all tablet formulations of thyroxine in the United Kingdom were of equivalent effectiveness. These concerns were mirrored by an increasing number of Adverse Drug Reaction (ADR) reports; mainly describing a lack of efficacy; interchangeability issues; and non-specific symptoms such as fatigue, alopecia and pain. The MHRA report was careful to point out that number of ADR reports remained extremely low compared with the number of patients taking thyroxine.

Selected relevant conclusions from the report are:

- Whilst recognising the difficulties in establishing bioequivalence for levothyroxine as an endogenous substance, bioequivalence studies in line with the FDA guidelines are of value in providing some reassurance of bioequivalence. (FDA guidelines recommend use of a supra-therapeutic dose of 600 µg and an acceptance interval of 80% to 125%.)
- Levothyroxine sodium has atypical solution properties and an extremely slow intrinsic dissolution rate.
- The in vivo absorption of levothyroxine products is dissolution rate limited.
- Formulation and manufacturing changes should be supported by bioequivalence studies.

Experience with new Eltroxin formulation in New Zealand

In New Zealand, a new formulation of Eltroxin was launched in 2007. This was for 50 µg and 100 µg tablets. The 50 µg tablet is the same formulation as the tablet proposed for registration in the current submission to the TGA but the 100 µg tablet differs in the quantity of excipients. In New Zealand, ADR reports started being received by Medsafe soon after launch: 39 between October 2007 and May 2008; and following media attention, 1309 between June 2008 and October 2008. There was also a (unsuccessful) petition submitted to the New Zealand House of Representatives requesting that Medsafe re-introduce the old version of Eltroxin and that Pharmac subsidise the old version.

A MHRA review of Medsafe procedures noted that the largest number of ADR reports was received in September 2008, probably in response to pressure groups.⁵ Also, a tick-box form was developed for patients on the internet, which might have increased the number of ADR reports. Specific symptoms reported included, alopecia (42), arthralgia (108), confusion (114), depression (151), headache (485), hypertension (45), lethargy (210), memory loss (84), palpitations (126), myalgia (190) and weight loss (205).

⁴ MHRA. Levothyroxine Tablet Products: A Review of Clinical and Quality Considerations. MHRA, 2013

⁵ MHRA, Expert Review of Medsafe's pre-licensing assessment and pharmacovigilance activities for a new formulation of ELTROXIN 50 µg and 100 µg tablets. MHRA, 2009, p18

Of the serious ADR reports, 5 of the 8 resulting in hospitalisation described symptoms that could be attributed to a thyrotoxic state. Excess levels of thyroxine were probably related to patients taking a mixture of the old and new formulations, patients frequently switching between formulations, and self-adjustment of dose.

In October 2008, two alternative brands of thyroxine were approved in New Zealand: Goldshield Levothyroxine and Synthroid (Abbott).

Quality

The pharmaceutical chemistry evaluator did not recommend registration because Eltroxin is less bioavailable than Oroxine/Eutroxsig and therefore cannot be considered a generic of Oroxine/Eutroxsig.

The quality evaluator points out that the proposed tablets are a different formulation to the registered tablets and are manufactured by a different method: direct compression versus wet granulation. These changes were made to increase the stability of the tablets (no need for refrigeration). However, a consequence of the new formulation is that the extent and rate of dissolution is less than for the registered reference product (Oroxine/Eutroxsig). The quality evaluator also had concerns about the proposed dissolution test method.

Study ARL/11/201 compared 600 µg (3x 200 µg tablets) of Eltroxin versus 600 µg (3x 200 µg tablets) of the registered reference product. For uncorrected total T4, the results for the ratio for Eltroxin/reference were: $AUC_{0-t}=89.1\%$ (90% CI: 84.7%, 93.7%); $C_{max}=86.2\%$ (82.1%, 90.6%). The 90% CI meet standard bioequivalence criteria (80% to 125%) but there are questions about whether thyroxine is a narrow therapeutic index drug and whether baseline correction should be used (see *Background* [above] and *Clinical Evaluation* [below]).

The quality evaluator concluded that Eltroxin had lower bioavailability than the registered reference product and that this is most likely the result of the different formulation and the lower extent and rate of dissolution. That is, the different formulation increases stability (Eltroxin does not require refrigeration), but the trade-off is that it is less bioavailable.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator recommended that approval be refused because all the strengths proposed for registration carry the risk of dose error if they are used interchangeably on a same-dose basis with the product currently marketed in Australia.

Efficacy

Two clinical studies were submitted:

- ARL/11/196: intended to assess dose proportionality for the 50 µg, 100 µg and 200 µg Eltroxin tablets
- ARL/11/201: intended to assess bioequivalence between Eltroxin and the reference registered product, Oroxine

ARL/11/196**Table 9. Summary of Study ARL/11/196**

Participants	67 healthy adults
Site	Single centre in India (Aug-Dec 2011)
Comparison	12x50 µg versus 6x100 µg versus 3x200 µg
Design	Single dose, fasting, 3-period, 3-treatment, cross-over

Table 10. Geometric mean and 90% confidence interval of baseline uncorrected total (bound+free) T4 (n=67)**Comparison of Test A with Test B for Total (bound+free)T4 (Uncorrected):**

Parameters	*Geometric Mean		% Ratio	90 % Confidence Interval for Log-transformed data	
	Test (A)	Test (B)	A/B	Lower Limit	Upper Limit
AUC ₀₋₄	424.496	404.556	104.9287	101.5467	108.4233
C _{max}	11.816	10.972	107.6953	104.6300	110.8505

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.

Comparison of Test C with Test B for Total (bound+free)T4 (Uncorrected):

Parameters	*Geometric Mean		% Ratio	90 % Confidence Interval for Log-transformed data	
	Test (C)	Test (B)	C/B	Lower Limit	Upper Limit
AUC ₀₋₄	417.882	404.556	103.2940	99.9647	106.7342
C _{max}	11.471	10.972	104.5559	101.5799	107.6191

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.

Corrected T4 results were not reported.

ARL/11/201**Table 11. Summary of Study ARL/11/201**

Participants	31 healthy adults
Site	Single centre in India (Sep-Nov 2011)
Comparison	3x200 µg Eltroxin versus 3x200 µg Oroxine
Design	Single dose, fasting, 2-period, 2-treatment, cross-over

As reported under *Quality* above: The uncorrected total T4 results for the ratio for Eltroxin/reference were:

AUC_{0-t}=89.1% (90% CI: 84.7%, 93.7%); C_{max}=86.2% (82.1%, 90.6%).

The corrected total T4 results for the ratio for Eltroxin/reference were:

AUC_{0-t}=74.0% (90% CI: 68.8%, 79.6%); C_{max}=74.1% (68.3%, 80.4%).

Safety

No specific data were submitted. The safety profile of thyroxine is well known. The key safety issue for this submission is whether Eltroxin is interchangeable on a same-dose basis with Oroxine/Eutroxisig.

First round clinical evaluator's recommendation

The First Round clinical evaluator proposed that approval of the products should be refused.

Risk management plan

European RMP (version 1, data lock point 12 October 2012) with Australian Specific Annex (version 0.1, dated 11 March 2013), to be revised to the satisfaction of the TGA, must be implemented.

Risk-benefit analysis

Delegate's considerations

In most overseas countries at least 3 different brands of thyroxine are available. In Australia however only one formulation of thyroxine tablet is available and it is marketed under two different names (Oroxine/Eutroxsig). The sponsor of the currently marketed thyroxine formulation in Australia (Aspen) has now applied to register a new thyroxine formulation (Eltroxin). The advantage of the new formulation is that it does not require refrigeration. The disadvantage of the new formulation is that it has a different dissolution profile and is less bioavailable than the formulation currently marketed in Australia.

Establishing the bioequivalence and interchangeability of two thyroxine tablets is not straight forward.^{4,6 7} A recent MHRA report (2013) reviewed the relevant literature but could not make any conclusions about whether thyroxine was a narrow therapeutic index drug or whether T4 levels should be baseline adjusted.

If, we make the strong assumption that thyroxine is not a narrow therapeutic index drug and that T4 levels do not need to be baseline adjusted, then Eltroxin meets the acceptance intervals for bioequivalence to Oroxine/Eutroxsig ($AUC_{0-t}=89.1\%$ [90% CI: 84.7%, 93.7%]). However, the 90%CI is all on the low side of 100%, indicating that Eltroxin is less bioavailable than Oroxine/Eutroxsig. This is consistent with the dissolution profile. That is, even using the weakest criteria for bioequivalence (based on the two strong assumptions listed above), the submitted data do not support the conclusion that Eltroxin is interchangeable on a same-dose basis with Oroxine/Eutroxsig.

If we were to require that the T4 levels should be baseline adjusted (as some clinical pharmacologists and endocrinologists would), then the acceptance interval for bioequivalence is not met ($AUC_{0-t}=74.0\%$ [90% CI: 68.8%, 79.6%]).

If we consider that thyroxine is a narrow therapeutic index drug (which is the view of some clinical pharmacologists and endocrinologists), then Eltroxin does not meet the criteria for bioequivalence to Oroxine/Eutroxsig (low boundary of the 90% CI for the (not baseline adjusted) ratio of AUC (84.7%) is lower than the low boundary of the acceptance interval for narrow therapeutic index drugs (90%).

An additional factor is the experience in New Zealand when the formulation of (old) Eltroxin was changed to the formulation of Eltroxin proposed for registration in Australia. A sudden increase in ADRs reported coincided with the launch of the new formulation.

⁶ Dong BJ, Hauck WW, Gambertoglio JG, Gee L, White JR, Bupp JL, Greenspan FS Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. JAMA. 1997 Apr 16;277(15):1205-13.

⁷ Colucci P, Seng Yue C, Ducharme M, Benvenga S. A Review of the Pharmacokinetics of Levothyroxine for the Treatment of Hypothyroidism. European Endocrinology, 2013;9(1):40-47

In short, the Delegate's preliminary view, at this point in time and pending ACPM advice, is that Eltroxin is not interchangeable on a same dose basis with Oroxine/Eutroxsig. That is, it cannot be considered a generic of Oroxine/Eutroxsig. The data submitted in the application show that the ("new") formulation of Eltroxin means that the thyroxine contained in the tablets is less bioavailable than the thyroxine in Oroxine/Eutroxsig.

Delegate's summary of issues

Eltroxin has a different formulation from the reference registered product (Oroxine/Eutroxsig), which means that it does not require refrigeration; however, the trade-off is that it has a different dissolution profile and is less bioavailable.

Based on the data provided by the sponsor in the submission both the quality evaluator and the clinical evaluator concluded that Eltroxin is not interchangeable, on a same-dose basis, with Oroxine/Eutroxsig.

Delegate's proposed action

The Delegate was not in a position to say, at this time, that Eltroxin should be approved as interchangeable on a same-dose basis with Oroxine/Eutroxsig.

At this point in time and pending ACPM advice, the Delegate's preliminary assessment was that registration Eltroxin might be allowed without it being interchangeable, on a same-dose basis, with Oroxine/Eutroxsig. That is, it might be considered equivalent, with dose adjustment. However, given documented problems with formulation changes of thyroxine in other countries, the Delegate was concerned that introduction of Eltroxin onto the Australian market could mean that current patients, who switch to Eltroxin, could be under dosed or over dosed; this would need to be carefully managed and monitored. The Delegate was also concerned about the possible removal of the current thyroxine product (Oroxine/Eutroxsig) from the Australian market and how current patients (stable on Oroxine/Eutroxsig) would transition to Eltroxin.

Conditions of registration

Implement the European RMP (version 1, data lock point 12 October 2012) with Australian Specific Annex (version 0.1, dated 11 March 2013) and any revisions requested by the TGA.

Revise the dissolution method so as to ensure the dissolution method is sufficiently discriminative. Revise the manufacturing process to the satisfaction of the TGA, so as to ensure that the tablet hardness throughout the shelf life will be such as to ensure compliance with the proposed dissolution limits (*using the discriminative dissolution method required*). Together these steps will ensure the bioequivalence of future batches of tablets to the batch tested against the innovator.

Delegate's request for ACPM advice

1. Does the ACPM consider that the sponsor has submitted sufficient evidence to establish that Eltroxin is a generic of Oroxine/Eutroxsig and could be used interchangeably, on a same-dose basis, with Oroxine/Eutroxsig?
2. If Eltroxin is not interchangeable on a same dose basis with Oroxine/Eutroxsig, does the ACPM consider the sponsor has submitted sufficient evidence such that Eltroxin could be registered as being equivalent to Oroxine/Eutroxsig, with dose adjustment?
3. Given the documented problems in New Zealand, what information should the PI/CMI contain? Is a Dear HealthCare Provider letter needed? If so, what information should it

contain? Are any other activities required (for example, information on the TGA website, interaction with professional organisation/colleges)?

4. The ACPM is requested to provide expert clinical advice on whether any clinical aspects of PI need refreshing.
5. On a separate, but related matter, the sponsor has advised the TGA of plans to withdraw the currently marketed formulation (Oroxine/Eutroxsig). The ACPM is asked to provide advice on any problems that this might cause for prescribers and patients; and how these might be avoided. Is a Dear HealthCare Provider letter needed? If so, what information should it contain? Are any other activities required (for example, information on the TGA website, interaction with professional organisation/colleges)?
6. Does the ACPM have any advice on the evidential standards for registration of thyroxine products; in particular whether thyroxine should be considered a narrow therapeutic index drug and whether T4 levels should be baseline corrected?

Delegate's questions for sponsor

- Does the sponsor have any update on the regulatory status of Eltroxin in EU, US, South Africa and Brazil?
- Has the sponsor had any discussions/meetings with the EMA or FDA about the current formulation of Eltroxin; and if so, what was the outcome?
- Could the sponsor provide a Dear HealthCare Provider letter, for editing by the TGA and consideration by the ACPM, that explains to prescribers the dose adjustment required for Eltroxin versus Oroxine/Eutroxsig?
- Does the sponsor have any details on the timeline for withdrawal of Oroxine/Eutroxsig from the Australian market?
- Could the sponsor provide a Dear HealthCare Provider letter, for editing by the TGA and consideration by the ACPM, that explains to doctors of patients currently taking Oroxine/Eutroxsig, how to manage the switch to Eltroxin? (should Oroxine/Eutroxsig be withdrawn)

Response from sponsor

Quality evaluation

Conditions for registration:

"Revise the dissolution method [information redacted] so as to ensure that the dissolution method is sufficiently discriminative. Revise the manufacturing process to the satisfaction of the TGA, so as to ensure that the tablet hardness throughout the shelf life will be such as to ensure compliance with the proposed dissolution limits (using the discriminative dissolution method required). Together these steps will ensure the bioequivalence of future batches of tablets to the batch tested against the innovator."

Email from TGA to Aspen Australia.

"Therefore unless you have bio-data to show that the hardness does not influence the bioavailability, you should use the dissolution method [information redacted] and review your manufacturing process to ensure the tablet hardness will not be at an unacceptable level on manufacture or rise to an unacceptable level during storage. An unacceptable level for hardness being one where the dissolution will not [information redacted]."

Alternatively, you could retain the [information redacted] method if the limit was at an earlier time [information redacted] or if you added an additional dissolution limit

[information redacted]. Both of these actions will have the effect of increasing the discriminative power of the test so that it is equivalent to NLT [information redacted]."

In order to increase the discriminative power of the dissolution test, the sponsor agrees with the evaluator's proposal to retain the paddle speed and set the dissolution limit at an earlier time point. This is in addition to the earlier proposal of increasing the Q value for release and on stability.

Stability data from the current studies on the 25 µg strength batches were assessed in order to provide assurance that the product range can meet this revised limit at the earlier time point. Samples of the 25 µg strength batches (packed in 200's) stored at 30°C/65% RH were evaluated following 24 months storage (end of shelf-life). The remaining strengths were not evaluated since the trials were well beyond the 24 month shelf-life (approaching 36 months storage).

In order to ensure that the tablet hardness throughout the shelf life will be such as to ensure compliance with the proposed dissolution limits, the sponsor proposes to revise the hardness specification for the product range.

Dissolution data has been generated on a batch of Eltroxin 50 µg, to assess the effect of the lower hardness on the release of the product at the earlier time points and to confirm that the friability of the tablet is not adversely affected.

The release profiles of the tablets compare favourably with the Oroxine reference products. Dissolution tests confirmed the evaluator's observation that dissolution slows with increase of hardness of tablets.

The tablets are suitably robust and the friability specification is still met at the lower hardness range.

The sponsor is confident that by revising the manufacturing process which leads to adjusting the hardness limits, and by increasing the discriminatory power of the dissolution test, the product is capable of meeting the tighter controls required by the TGA in order to ensure bioequivalence of future batches of Eltroxin tablets to the innovator.

RMP evaluation

It is recommended that 'change in clinical response when switching brands' be added as an 'important potential risk' in the Australian-specific annex.

The sponsor believes that the existing identified risk of 'Treatment imbalance leading to hyperthyroidism and hypothyroidism' in the EU RMP, already considers the 'change in clinical response when switching brands'.

The identified risk of 'Treatment imbalance leading to hyperthyroidism and hypothyroidism' considers the following risk factors:

- Change from previous to new formulation
- Change of product from one brand to another brand
- Drug Interactions

The identified risk of 'Treatment imbalance leading to hyperthyroidism and hypothyroidism' considers the following risk groups where imbalance can have a severe impact on their condition:

1. Paediatric patients should be monitored closely to avoid under treatment or over treatment. Under treatment may have deleterious effects on intellectual development and linear growth. Overtreatment has been associated with craniosynostosis in infants, and may adversely affect the tempo of brain maturation and accelerate the bone age with resultant premature closure of the epiphyses and compromised adult stature.

2. Pregnancy: Hypothyroidism during pregnancy has been associated with impaired cognitive development and increased fetal mortality. During pregnancy, maternal thyroid hormone requirements increase. Although it is known that women with hypothyroidism should increase their levothyroxine dose during pregnancy, biochemical hypothyroidism occurs in many.
3. Elderly people : for cardiac toxicity and risk of fracture
4. Patients with medical history of cardiac disorders : Increased thyroxine levels could lead to atrial fibrillation and other arrhythmias
5. Patients with diabetes mellitus or insipidus
6. Patients with nontoxic diffuse goitre or nodular thyroid disease
7. Patients with a previous history of thyroid cancer. Low levels of levothyroxine could lead to an unexpected increase in TSH and recurrence of thyroid cancer.

The following updates have been made to the EU RMP since that submitted with the sponsor's response to the TGA:

- point 4 has been re-worded from simply 'cardiac patients', and
- point 7 has been added.

Clinical evaluation

Lack of adjustment for baseline T4 levels

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).

Aspen acknowledges the comments from the MHRA report (2013), the FDA transcript (2005) and the EMA guideline on bioequivalence. The EMA guideline on investigation of bioequivalence, also states that "*In rare cases where substantial increases over baseline endogenous levels are seen, baseline correction may not be needed*".

Levothyroxine is considered as a separate class of endogenous substance and needs to be considered as a special case due to the following scientific facts.

Fact A: Levothyroxine has a half-life of approximately 6 to 9 days in healthy individuals.

Fact B: Since levothyroxine has a long half-life, T4 levels remain fairly static and are not greatly affected by circadian rhythm.

Fact C: When a hyper physiologic dose of levothyroxine sodium is given to a healthy subject, as in the case of the BA/BE studies in this submission and because of the extreme sensitivity of the thyroid hormone regulatory system to subtle changes in T4 levels, endogenous T4 production and secretion approaches zero within 1 hour. Subsequently, as exogenous T4 levels begin to approach normal physiologic values, endogenous production and secretion resumes. These facts suggest that baseline-uncorrected data would more accurately represent the endogenous environment and in view of this, baseline correction is not appropriate for establishing bioequivalence, irrespective of whether there is an increase or decrease in the endogenous levels over baseline levels. Hence, baseline uncorrected data is considered a more reliable measure for establishing bioequivalence for levothyroxine.

As per the FDA guidance and protocol, a 90% Confidence Interval needs to be established for C_{max} and AUC_{0-t} for uncorrected total T4 (TT4), and this data was presented in the bioequivalence study report.

However, as per the request from the evaluator, the 90% CI for corrected TT4 has been presented for AUC_{0-48} , AUC_{0-t} and C_{max} using the baseline corrected method described in section a) below. The data is presented in the table in section b) below.

a) Method used to report the baseline adjustment:

The predefined procedure as per protocol was followed for baseline corrections.

Baseline concentrations were determined from blood samples collected at -0.50, -0.25, 0.00 hours predose for each dosing period. The baseline concentrations are period specific. The average of the above mentioned three values was calculated for each subject and was taken as the baseline value for that subject.

The corrected serum concentrations were obtained after subtracting the baseline values from the observed serum Total (bound + free) T3 and T4, free T3 and T4 values at all post dose time points for each subject. If a negative serum concentration value resulted after baseline correction, this was set to 0, prior to calculating the baseline-corrected AUC. In the case of a 0 value occurring between two measurable concentrations, this was treated as a 'missing value' (as per the Standard operating Procedure (SOP)) for pharmacokinetic and statistical analysis and calculation of the statistical analysis proceeded as per protocol requirements.

b) 90% CI for baseline corrected TT4 for AUC_{0-48} , AUC_{0-t} and C_{max}

Table 12. ARL/11/201-BE results for corrected TT4

ARL/11/201-BE RESULTS FOR CORRECTED TT4									
Dependent	Test	FormRef	TestGeotS	RefGeotSN	Ratio%Ref	CI_90_Lower	CI_90_Upper	Power (%)	ISV (%)
ln(AUC48)	A	B	155.60	207.58	74.96	70.16	80.10	100.00%	15.43%
ln(AUCLAST)	A	B	153.69	207.58	74.04	68.84	79.63	100.00%	16.97%
ln(CMAX)	A	B	5.71	7.70	74.09	68.27	80.39	100.00%	19.09%

Note: There is a slight difference in AUC_{0-t} and AUC_{0-48} values, due to a missing sample (48 h sampling point) for one subject.

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.

Is thyroxine a narrow therapeutic index drug? The sponsor was invited to comment on this issue.

There have been varied views on whether or not levothyroxine is a narrow therapeutic index drug and this is being debated by various clinical endocrinologists. Since there is no specific definition for Narrow Therapeutic Index (NTI) drugs in the TGA and EMA guidelines, the sponsor concludes that Levothyroxine is not an NTI drug, considering the following facts:

1. The difference between minimum toxic and minimum effective concentrations of levothyroxine is more than two fold.
2. Acute toxicity and a possible need for therapeutic dose monitoring are usually key characteristics of NTI drugs in practice. However, studies have been conducted using a suprathreshold dose of 600 µg (three times the patient's daily dose) under direct observation, where there were no serious safety issues. Even in this current study (ARL/11/201), the dose of 600 µg was well tolerated and there were no safety issues encountered.

Therefore, acute toxicity with well over thrice the daily requirement of levothyroxine did not pose safety risks, at least over the short term. In this sense, levothyroxine does not fall into the NTI category.

Delegate's overview - Questions for the sponsor

Does the Sponsor have any update on the regulatory status of Eltroxin in the EU, US, South Africa and Brazil? Updated information is provided under section A3b-International regulatory history.

Has the sponsor had any discussions/meetings with the EMA or FDA about the current formulation of Eltroxin; and if so, what was the outcome? There have been no discussions/meetings between with the EMA or FDA.

As a result of the ongoing evaluation in the EU we have received the Day 120 draft assessment report from the Reference Member State (The Netherlands) on 10 Jan 2014. Although this application is still in progress the assessment report contains the following:

- Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Levothyroxin Vale could be approvable provided that satisfactory responses are given to the preliminary list of questions.
- Section V includes five questions. One question relates to the tightening of the dissolution specification. The dissolution methodology has been accepted.
- The RMS has accepted the bioequivalence study results and the biowaiver requests for the lower strengths.

As a result of the ongoing evaluation in the US the sponsor has received the assessment on the dissolution testing portion of our submission. Aspen is in the process of generating the additional dissolution data requested and preparing a response to this deficiency letter.

It is Aspen's intention to approach the USP and request inclusion of our dissolution method in the pharmacopoeia. Contact has been made with the USP and the process will be initiated once the FDA has accepted our dissolution method.

Could the sponsor provide a Dear Healthcare Provider letter, for editing by the TGA and consideration by the ACPM, that explains to prescribers the dose adjustment required for Eltroxin versus Oroxine/Eutroxsig?

A draft Dear HealthCare Provider letter was included in the sponsor's response.

Does the sponsor have any details on the timeline for withdrawal of Oroxine/Eutroxsig from the market?

In order to cooperate with the TGA, Aspen is prepared to keep Oroxine/Eutroxsig on the Australian market.

Could the sponsor provide a Dear HealthCare Provider letter, for editing by the TGA and consideration by the ACPM, that explains to doctors of patients currently taking Oroxine/Eutroxsig, how to manage the switch to Eltroxin? (should Oroxine/Eutroxsig be withdrawn).

Aspen agrees to maintain Oroxine/Eutroxsig on the Australian market.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new generic medicine and a major variation (strength) for a currently registered product.

The ACPM resolved to recommend to the TGA delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Eltroxin / Aspen Thyroxine / Thyroxine Aspen tablet containing 25 µg, 50 µg, 75 µg, 88 µg, 100 µg, 112 µg, 125 µg, 137 µg, 150 µg, 175 µg and 200 µg of levothyroxine sodium to have an overall positive benefit–risk profile for the amended indication;

Eltroxin is indicated for

- *management of demonstrated thyroid hormone deficiency*
- *suppression of thyrotropin (TSH) for the management of TSH-responsive tumours of the thyroid*

The ACPM advised that 'Eltroxin has also been used in the management of thyroiditis such as Hashimoto's disease' is redundant; it may have been necessary prior to the development of TSH assays. The indication '*demonstrated thyroid hormone deficiency*' includes raised TSH in mild (primary) thyroid failure as well as overt clinical and biochemical hypothyroidism, and the various degrees of secondary hypothyroidism.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA.
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on some inclusions for the PI, the details of these are however are beyond the scope of this AusPAR.

Specific advice

1. *Does the ACPM consider that the sponsor has submitted sufficient evidence to establish that Eltroxin is a generic of Oroxine/Eutroxsig and could be used interchangeably, on a same-dose basis, with Oroxine/Eutroxsig?*

The ACPM advised that, from the evidence submitted,

- Eltroxin is not bioequivalent to the currently available products, Oroxine / Eutroxsig
 - is therefore not interchangeable dose for dose with Oroxine / Eutroxsig
 - is not a generic equivalent of Oroxine/Eutroxsig.
2. *If Eltroxin is not interchangeable on a same-dose basis with Oroxine/Eutroxsig, does the ACPM consider the sponsor has submitted sufficient evidence such that Eltroxin could be registered as being equivalent to Oroxine/Eutroxsig, with dose adjustment?*

The ACPM was of the view that Eltroxin could be registered as being an alternative to Oroxine/Eutroxsig. The evidence provided demonstrated Eltroxine has a positive benefit:risk profile for the requested indications (as modified) but that the dose required would need titrating.

3. *Given the documented problems in New Zealand, what information should the PI/CMI contain? Is a Dear HealthCare Provider letter needed? If so, what information should it*

contain? Are any other activities required (for example, information on the TGA website, interaction with professional organisation/colleges)?

The ACPM recommended that a “Dear HealthCare Provider Letter” is required and the letter should reference the bioavailability data which suggest that slightly higher doses may be required than the currently registered product. The ACPM noted that the proposed letter declares switching from one product to another should be avoided unless necessary and that when switching, thyroid function tests should be obtained. The ACPM noted the New Zealand experience and recommended that the specific advice in the Dear HealthCare provider letter should also be included in the PI, particularly the reference to avoid switching, the bioavailability data and the need for careful monitoring. The PI/CMI should contain information that Eltroxin is not interchangeable with the currently marketed product Oroxine/Eutroxsig and that restabilisation is required.

4. *The ACPM is requested to provide expert clinical advice on whether any clinical aspects of PI need refreshing.*

- The ACPM recommended the revisions as stated above.
- The CMI should also be refreshed to reflect the new information in the PI.
- For therapeutic guidelines recommendations: In adult patients under 60 years, in the absence of ischaemic heart disease, commence with:
 - thyroxine 50 to 100 µg orally, daily, increasing the daily dose by 25 to 50 µg according to response at not less than 4-weekly intervals, up to 100 to 200 µg daily.

5. *On a separate, but related matter, the sponsor has advised the TGA of plans to withdraw the currently marketed formulation (Oroxine/Eutroxsig). The ACPM is asked to provide advice on any problems that this might cause for prescribers and patients; and how these might be avoided. Is a Dear HealthCare Provider letter needed? If so, what information should it contain? Are any other activities required (for example, information on the TGA website, interaction with professional organisation/colleges)?*

The ACPM noted that the sponsor declared in the pre-ACPM response that it is prepared to keep Oroxine/Eutroxsig on the market. This was approved by the ACPM, especially in light of the need to re-titrate many patients and increase monitoring in the short term.

6. *Does the ACPM have any advice on the evidential standards for registration of thyroxine products; in particular whether thyroxine should be considered a narrow therapeutic index drug and whether T4 levels should be baseline corrected?*

The ACPM recommended that thyroxine should be considered an atypical narrow therapeutic index drug and that T4 Levels should be baseline corrected.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Eltroxin, Aspen thyroxine and Thyroxine Aspen tablets, containing levothyroxine sodium; 25, 50, 75, 88, 100, 112, 125, 137, 150, 175 and 200 µg, for oral administration, indicated for:

Eltroxin is indicated for the management of demonstrated thyroid hormone deficiency.

Eltroxin is also used to suppress thyrotropin (TSH) for the management of TSH-responsive tumours of the thyroid.

Specific conditions of registration applying to these goods

1. The Levothyroxine Sodium EU Risk Management Plan (RMP) version I (data lock point 12 October 2012) with Australian Specific Annex (version 0.1, dated 11 March 2013) and any subsequent revisions, as agreed with the TGA will be implemented in Australia. An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is no less than three years from the date of this approval letter. No fewer than three annual reports are required.
2. A Dear Healthcare Provider' (DHCP) letter (with wording as approved by TGA) is to be distributed at the time of launch of the products.

Attachment 1. Product Information

The Product Information approved for main Eltroxin at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>. The PIs for Aspen Thyroxine and Thyroxine Aspen are identical except for the product name.

Attachment 2. Extract from the Clinical Evaluation Report

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