CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202231Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	202-231
Submission Dates	August 30, 2010 and December 20, 2010
Brand Name	*To be determined*
Generic Name	Levothyroxine sodium
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Sally Y. Choe, Ph.D.
OCP Division	Clinical Pharmacology 2 (HFD 870)
OND Division	Metabolism and Endocrinology Products (HFD 510)
Sponsor	APP Pharmaceuticals
Formulation; Strengths	Intravenous injection; 100, 200, and 500 µg/vial
Relevant IND	101,385
Indications	Treat myxedema coma (b) (4)

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1 Executive Summary

The sponsor is currently the sole supplier of levothyroxine sodium injection (200 and 500 µg/vial) to treat hypothyroid patients.

The Food and Drug Administration (FDA) categorized levothyroxine sodium injection a "Marketed Unapproved Drug," thus requiring a New Drug Application (NDA) submission and an approval in order to continue marketing the product. The sponsor received such an FDA Warning Letter on December 18, 2006. In compliance with the requirement, the sponsor submitted a 505(b)(2) NDA for their levothyroxine sodium injection without conducting any clinical studies to seek an approval for the indications of the treatment of myxedema coma, (b) (4) The sponsor relies only on published literature to support this NDA.

1.1 Recommendations
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 202-231's Clinical Pharmacology data and finds it acceptable.

1.2 Post Marketing Requirement or Post Marketing Commitment
None.

1.3 Summary of Important Clinical Pharmacology Findings
Although the sponsor did not conduct any study to demonstrate the in vivo bioavailability of their levothyroxine sodium injection and there is no FDA-approved levothyroxine sodium injection for the sponsor to refer, the requirement of in vivo bioavailability data for the sponsor's levothyroxine sodium injection may be waived for good cause so as to protect the public health per the CFR Section 320.22(e), since levothyroxine sodium injection is a medically necessary drug and is intravenously administered.

The review team mulled over the need of relative bioavailability information between intravenous levothyroxine sodium injection and oral levothyroxine sodium product so as to help clinicians transition patients from intravenous to oral dosing. For myxedema coma patients, the need for this relative bioavailability information is not as critical since:

- In clinical practice, it is generally understood that the intravenous dose is typically 50% of the oral dose. Therefore, clinicians can follow this practice when initiating oral levothyroxine.
- In general, when initiating oral levothyroxine, it is standard of care to reassess a patient clinically and with laboratory data at a minimum of 6 weeks after the drug is started. Therefore, unless a patient did not follow-up with their clinician, it would be unlikely that a patient would remain at a suboptimal oral dose for an extended period of time.

Thus, the relative bioavailability information between intravenous levothyroxine sodium injection and oral levothyroxine sodium product is "nice to have" and not "need to have" for myxedema coma patients. However, this relative levothyroxine bioavailability information may be critical for other indications such as hypothyroid patients who temporarily cannot take oral levothyroxine sodium products and have to be transitioned to intravenous administration.

Upon intravenous administration, levothyroxine rapidly distributes to tissues. Levothyroxine is more than 99% plasma protein bound, which protects the hormone from metabolism and excretion as well as resulting in a long half-life in the systemic circulation (about 6 – 8 days for euthyroid patients and 9 – 10 days for myxedema patients). The major pathway of thyroid hormone metabolism is via sequential deiodination. Thyroid hormones are primarily eliminated by the kidneys.

Both published mechanistic and clinical studies support the proposed intravenous levothyroxine sodium initial loading dose of 300 – 500 μg and maintenance dose of 50 – 100 μg once daily for myxedema coma.

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S.W. Johnny Lau, R.Ph., Ph.D.
OCP/DCP2

FT signed by Sally Y. Choe, Ph.D., Team Leader, 5/ /11

An Office Level Clinical Pharmacology Briefing for NDA 202-231 was conducted on April 29, 2011; participants included N. Lowy, D. Roman, A. Rahman, G. Burckart, L. Lesko, H. Ahn, D. Abernethy, L. Galgay, C. Sahajwalla, L. Jain, C. Shukla, J. Leginus, A. Agrawal, Z. Li, L. Zhao, K. Reynolds, R. Jain, I. Zadezensky, S. Naraharisetti, A. Khandelwal, Y. Mulugeta, J-E Lee, J. Bishai, S. Choe, and J. Lau.

2 Question-Based Review

The sponsor did not conduct any clinical pharmacology study and they relied only on published literature to support NDA 202-231.

2.1 Bioavailability Requirement

What is the requirement for the bioavailability of levothyroxine sodium injection?

Regulatory Requirement

Per the Code of Federal Regulation (CFR) 320.21 "Requirements for submission of bioavailability and bioequivalence data."

(a) Any person submitting a full new drug application to the Food and Drug Administration (FDA) shall include in the application either:

(1) Evidence measuring the in vivo bioavailability of the drug product that is the subject of the application; or

(2) Information to permit FDA to waive the submission of evidence measuring in vivo bioavailability.

The sponsor does not have any in vivo bioavailability data for their levothyroxine sodium injection and by submitting the literature data, (2)'s waiver option can be applicable. Since this product is a parenteral solution intended solely for administration by injection, the following CFR can be applicable to the waiver:

CFR 320.22 "Criteria for waiver of evidence of in vivo bioavailability or bioequivalence."

(b) For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration **as a drug product that is the subject of an approved full new drug application** or abbreviated new drug application.

The missing critical information for this NDA is the underlined portion of the last 2 lines above. Because there is no approved levothyroxine sodium injection product as reference, this waiver is not applicable. Thus, the sponsor needs to conduct a study to characterize the bioavailability of their levothyroxine sodium injection to satisfy the CFR 320.21.

The Sponsor's Submission

The sponsor cited the Maxon et al. article (see Question 2.6.1 below) to provide the relative bioavailability data between SYNTHROID intravenous injection and SYNTHROID oral tablet as well as LEVOTHROID oral tablet (*Int J Clin Pharmacol Ther Toxicol* 1983;21:379-82). The Maxon et al. article could have provided the sponsor's to-be-marketed levothyroxine sodium injection bioavailability data via linking it to the oral levothyroxine bioavailability data. However, the NDA approval dates for SYNTHROID and LEVOTHROID oral tablets are July 24, 2002 and October 24, 2002, respectively (Drugs@FDA). Thus, Maxon et al. studied unapproved SYNTHROID and LEVOTHROID oral tablets before August 21, 1983 (publication date). Had the sponsor studied any approved oral levothyroxine products, they may satisfy the waiver requirement via linking the bioavailability of levothyroxine sodium injection to the bioavailability of an approved oral levothyroxine product(s).

The Sponsor, APP Pharmaceuticals, is currently the sole source of levothyroxine injection and therefore is supplying all intravenous levothyroxine demand of this medically necessary drug (Clinical Filing Checklist, October 19, 2010).

Balancing the need of the above issues, the Review Team recommended filing this NDA and Clinical Pharmacology requested the sponsor to respond to the following:
"We have noted that there is no drug exposure information of an approved levothyroxine injection product in your submission. If you have any information or data addressing this or any relative exposure information of your product comparing to that of an approved levothyroxine product (i.e., either injection product or oral tablet product), submit those information by December 20, 2010."

The sponsor confirmed on December 20, 2010 that the NDA does not contain "clinical drug exposure data for an approved levothyroxine injection product" because no such FDA approved product currently exists.

The Office of Clinical Pharmacology's Recommendations

CFR 320.22 "Criteria for waiver of evidence of in vivo bioavailability or bioequivalence."

(e) FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence if waiver is compatible with the protection of the public health. For full new drug applications, FDA may defer a requirement for the submission of evidence of in vivo bioavailability if deferral is compatible with the protection of the public health.

The Office of Clinical Pharmacology recommends a waiver for the sponsor to submit the in vivo bioavailability data of their levothyroxine sodium injection for good cause so as to protect the public health per the CFR Section 320.22(e), since levothyroxine sodium injection is a medically necessary drug and is intravenously administered.

The review team mulled over the need of relative bioavailability information between intravenous levothyroxine sodium injection and oral levothyroxine sodium product so as to help clinicians transition patients from intravenous to oral dosing. For myxedema coma patients, the need for this relative bioavailability information is not as critical since:

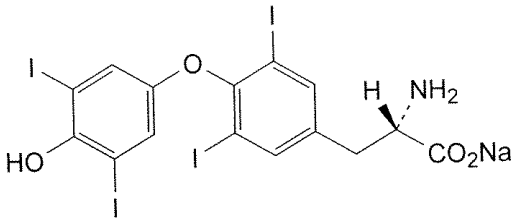
- In clinical practice, it is generally understood that the intravenous dose is typically 50% of the oral dose. Therefore, clinicians can follow this practice when initiating oral levothyroxine.
- In general, when initiating oral levothyroxine, it is standard of care to reassess a patient clinically and with laboratory data at a minimum of 6 weeks after the drug is started. Therefore, unless a patient did not follow-up with their clinician, it would be unlikely that a patient would remain at a suboptimal oral dose for an extended period of time.

Thus, the relative bioavailability information between intravenous levothyroxine sodium injection and oral levothyroxine sodium product is "nice to have" and not "need to have" for myxedema coma patients. However, this relative levothyroxine bioavailability information may be critical for other indications such as hypothyroid patients who temporarily cannot take oral levothyroxine sodium products and have to be transitioned to intravenous administration.

2.2 General Attributes

2.2.1 What are levothyroxine sodium's key physicochemical properties?

Figure 1. Levothyroxine sodium's molecular structure.



Levothyroxine sodium has a molecular weight of 798.85, empirical formula of $C_{15}H_{10}I_4NNaO_4$, and solubility of 15 mg/100 mL in water. Levothyroxine sodium has pKa values of 2.2, 6.7, and 10.1 and has 1 chiral center. The L-form of thyroxine is the active pharmaceutical ingredient.

2.2.2 What is the formulation for the to-be-marketed levothyroxine sodium injection?

Table 1. The to-be-marketed levothyroxine sodium injection formulation for the 100 µg strength.

Levothyroxine Sodium for Injection	Unit Dose	Exhibit Batches	Proposed Commercial Batch
Strength	**100 mcg/vial**		
Packaging Configuration	**100 mcg in a 6.5–mL vial**		
Product Code	**506107**		
Batch Size (L)	**N/A**	(b) (4)	
Batch Size (vials)	**N/A**		
Ingredient	**Ingredient Amount/mL**	**Ingredient Amount/Batch**	**Ingredient Amount/Batch**
Levothyroxine Sodium, USP	100 mcg	(b) (4)	
Dibasic Sodium Phosphate, Heptahydrate, USP	(b) (4)		
Mannitol, USP			
Sodium Hydroxide, NF			
(b) (4)			
(b) (4)			
Sodium Hydroxide, NF			
(b) (4)			

Table 2. The to-be-marketed levothyroxine sodium injection formulation for the 200 µg strength.

Levothyroxine Sodium for Injection	**Unit Dose**	**Exhibit Batches**	**Proposed Commercial Batch**
Strength	**200 mcg/vial**		
Packaging Configuration	**200 mcg in a 10–mL vial**		
Product Code	**24710**		
Batch Size (L)	**N/A**	(b) (4)	
Batch Size (vials)	**N/A**		
Ingredient	**Ingredient Amount/mL**	**Ingredient Amount/Batch**	**Ingredient Amount/Batch**
Levothyroxine Sodium, USP	200 mcg	(b) (4)	
Dibasic Sodium Phosphate, Heptahydrate, USP	(b) (4)		
Mannitol, USP			
Sodium Hydroxide, NF			
(b) (4)			
(b) (4)			
Sodium Hydroxide, NF			
(b) (4)			

Table 3. The to-be-marketed levothyroxine sodium injection formulation for the 500 µg strength.

Levothyroxine Sodium for Injection	**Unit Dose**	**Exhibit Batches**	**Proposed Commercial Batch**
Strength	**500 mcg/vial**		
Packaging Configuration	**500 mcg in a 10–mL vial**		
Product Code	**24810**		
Batch Size (L)	**N/A**	(b) (4)	
Batch Size (vials)	**N/A**		
Ingredient	**Ingredient Amount/mL**	**Ingredient Amount/Batch**	**Ingredient Amount/Batch**
Levothyroxine Sodium, USP	500 mcg	(b) (4)	
Dibasic Sodium Phosphate, Heptahydrate, USP	(b) (4)		
Mannitol, USP			
Sodium Hydroxide, NF			
(b) (4)			
(b) (4)			
Sodium Hydroxide, NF			
(b) (4)			

Tables 4. Explanation of the to-be-marketed levothyroxine sodium injection formulation.

Sponsor's Error! Reference source not found. Inactive Ingredients	Function of Inactive Ingredients
Dibasic Sodium Phosphate Heptahydrate, USP	(b) (4)
Mannitol, USP	
Sodium Hydroxide, NF	
(b) (4)	
(b) (4)	
1 Theoretical amount of Levothyroxine Sodium, USP required for the batch.	(b) (4)
(b) (4)	
2	(b) (4)

2.2.3 How does levothyroxine sodium injection work for the proposed indications?
Levothyroxine sodium injection works as a thyroid hormone replacement therapy for hypothyroidism.

2.2.4 What are the sponsor's proposed indication and dosing regimen for levothyroxine injection?
The proposed indications for levothyroxine sodium injection are the treatments of the following:

- myxedema coma

(b) (4)

The proposed dosing regimen for the intravenous levothyroxine sodium injection is the following:

- 300 – 500 µg as the initial loading dose
- 50 – 100 µg once daily as the maintenance doses until the patient can tolerate oral therapy

2.3 General Clinical Pharmacology
2.3.1 What are levothyroxine's clinical pharmacokinetic (PK) characteristics?
Absorption
The route of administration for levothyroxine sodium injection is intravenous. Upon administration, the administered synthetic levothyroxine is not distinguishable from the endogenous levothyroxine.

Distribution — Plasma proteins bound more than 99% of circulating thyroid hormones. These proteins include thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for levothyroxine partially explains the higher serum concentrations, slower metabolic clearance, and longer half-life of levothyroxine compared to liothyronine. Protein-bound thyroid hormones exist in reverse equilibrium with small amounts of free hormone. Only unbound hormone is metabolically active. Many drugs and physiologic conditions affect the binding of thyroid hormones to serum proteins. Thyroid hormones do not readily cross the placental barrier.

Metabolism — Elimination of levothyroxine is slow (see Table 6). The major metabolic pathway of thyroid hormone is via sequential deiodination. About 80% of circulating T_3 comes from peripheral levothyroxine monodeiodination. The liver is the major site of degradation for both levothyroxine and liothyronine, with levothyroxine deiodination also occurring at a number of additional sites, including the kidney and other tissues. About 80% of the daily levothyroxine dose is deiodinated to yield equal

amounts of liothyronine and reverse liothyronine. Liothyronine and reverse liothyronine are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

Table 6. Pharmacokinetic parameters of thyroid hormones in euthyroid patients

Hormone	Ratio in Thyroglobulin	Biologic Potency	$t_{½}$ (days)	Protein Binding (%)[¶]
Levothyroxine	10—20	1	6 – 8[‡]	99.96
Liothyronine	1	4	≤ 2	99.5

[‡] 3 to 4 days in hyperthyroidism, 9 to 10 days in hypothyroidism;; [¶]Includes TBG, TBPA, and TBA

These $t_{½}$ values are from the *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12th ed, Chapter 39, Thyroid and Anti-thyroid Drugs. This textbook's earlier editions (before the 10th ed) stated that euthyroid patients' $t_{½}$ is 6 – 7 days. Also, this textbook does not state the route of administration for these $t_{½}$ values. However, these $t_{½}$ values are consistent with the mean levothyroxine $t_{½}$ reported by Sterling and Chodos (*J Clin Invest* 1956;35:806-13), 6.7, 4.4, and 9.7 days, respectively, for normal, thyrotoxicosis, and myxedema patients upon intravenous administration of I^{131} levothyroxine.

Excretion — Thyroid hormones are primarily eliminated by the kidneys. A portion of the conjugated hormone reaches the colon unchanged and appears in the feces. About 20% of levothyroxine is eliminated in the stool. Urinary excretion of levothyroxine decreases with age.

The above information is modified from the recently approved label of a levothyroxine sodium tablet (http://www.accessdata fda.gov/drugsatfda_docs/label/2011/021301s027lbl.pdf).

2.3.2 Is levothyroxine PK dose-proportional upon intravenous administration?

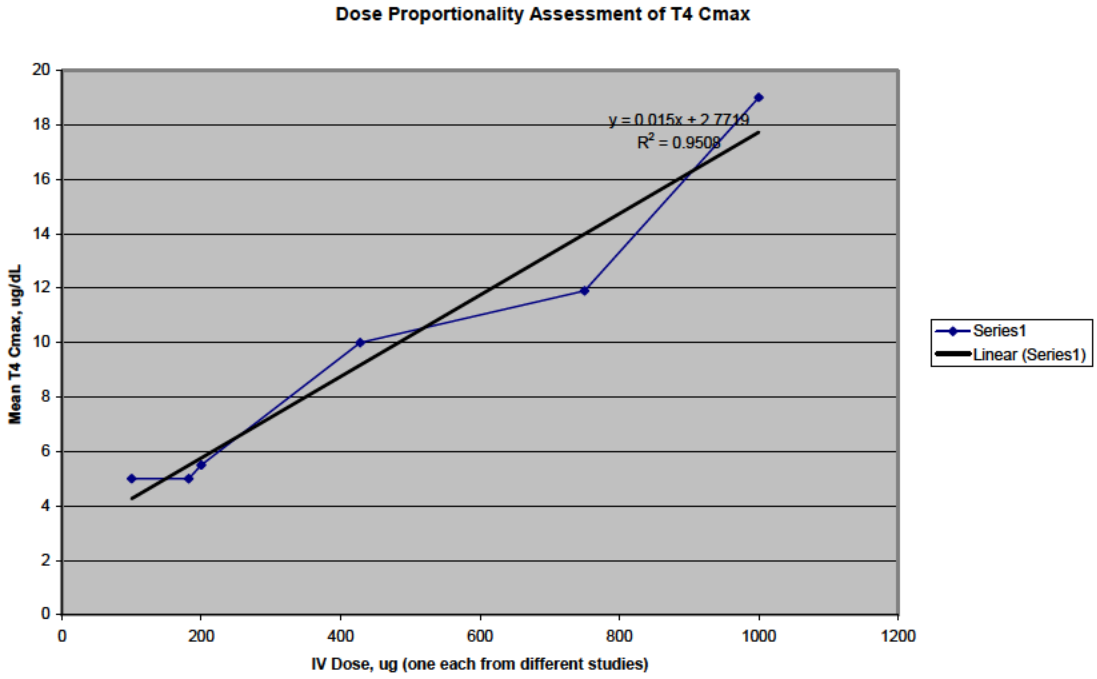
The sponsor claimed that intravenous levothyroxine shows dose proportional PK per Table 7's data on their December 20, 2010 submission.

Table 7. Levothyroxine dose and exposure summary.

Dose (µg)	Number of Patients Exposed	Average Free[‡] T_4 C_{max} (µg/dL)	Reference[¶]
100	17	5.0	?
182	5[*]	5.0	Maxon et al.
200	8	5.5	?
428	6	10.0	Ridgway et al.
750	7	11.9	?
1000	2	19.0	Arlot et al.
Mean Dose = 433	Total Exposures = 46		

[*]Healthy subjects; [‡]Reviewer noticed that this should be total rather than free T_4 C_{max} as stated in Summary of Clinical Pharmacology Studies' Table 2.7.2-3; [¶]Reviewer added this column to track the references; ?Reviewer could not confirm the data with reference.

Figure 2. Linear relationship between dose and C_{max} of levothyroxine.



The sponsor provided inadequate data to assess intravenous levothyroxine PK dose proportionality because:

- Each dose is from a different study, which has different input rate and thus affect C_{max}.
- AUC data are also necessary to determine PK dose proportionality besides C_{max} data.
- Each C_{max} is a mean value and does not reflect its variability.
- The dose and C_{max} values may be from a mix of single-dose and multiple-dose studies.

2.3.3 Do multiple intravenous administrations alter levothyroxine PK?

The exposure of levothyroxine shows gradual accumulation upon multiple-dose intravenous levothyroxine daily administration, which is consistent with levothyroxine's $t_{½}$ of 9 – 10 days (Ladenson et al. *Am J Med* 1982;73:467-74 and Ridgway et al. *Ann Intern Med* 1972;77:549-55).

2.3.4 How are the proposed daily intravenous levothyroxine sodium injection dosing regimen determined for myxedema coma patients?

Hovey et al. (*Arch Intern Med* 1964; 113:89-96) assumed the extrathyroid organic iodide pool is grossly depleted in myxedema patients and averages 245 µg/1.73 m^2, whereas that for euthyroid individuals averages 490 µg/1.73 m^2. Iodine comprises of 65.4% of levothyroxine by weight. Thus, a myxedema patient would have an average deficit of about 360 µg levothyroxine, which is consistent with the proposed intravenous loading dose of 300 – 500 µg levothyroxine sodium.

The fractional hormonal turnover rate is about 11% or 50 – 60 µg of hormonal iodine daily in euthyroid individuals. The fractional levothyroxine turnover rate is about 7% or 15 – 20 µg of hormonal iodine daily in myxedema patients. Repletion of the hormonal pool with large doses of levothyroxine does not restore the turnover rate to normal immediately. Intravenous administration of 500 µg levothyroxine to a myxedema coma patient would result in the initial utilization of an added 25 µg hormonal iodine daily. To restore the minimal euthyroid state, the average myxedema patient would need 40 – 50 µg hormonal iodine daily. This corresponds to 61 – 76 µg levothyroxine daily, which is consistent with the proposed intravenous maintenance dose of 50 – 100 µg levothyroxine sodium daily.

Table 8. Literature recommendations on the levothyroxine dosing regimen for myxedema coma.

Intravenous Loading Dose	Intravenous Daily Maintenance Dose	Reference
300 – 500 µg	50 – 100 µg	Mitchell et al. *Emerg Med Clin North Am* 1989;7:885-902
300 – 500 µg	50 – 100 µg	Fliers et al. *Rev Endocr Metab Disord* 2003;4:137-41
100 – 500 µg	75 – 100 µg	C.R. Wall (*Am Fam Physician* 2000;62:2485-90
300 µg	50 – 200 µg	J.D. Bagdale (*Med Clin North Am* 1986;70:1111-28
300 – 500 µg	75 – 125 µg	D.S. Cooper's chapter "Thyroid hormone replacement therapy for primary and secondary hypothyroidism" in Wayne Meike's "Endocrine replacement therapy in clinical practice" book, 2003 ed; this reviewer's citation

Both published mechanistic and clinical studies support the proposed intravenous levothyroxine sodium initial loading dose of 300 – 500 µg and maintenance dose of 50 – 100 µg once daily.

2.3.5 Exposure-Response

What is the evidence of exposure-response relationship for intravenous levothyroxine?

With the gradual increase in serum levothyroxine concentrations upon intravenous 100 µg levothyroxine daily dosing, there is the consistent decrease in serum thyrotrophin (TSH) concentrations as evidenced in 10 hypothyroid patients, Figure 3 (Ladenson et al. *Am J Med* 1982;73:467-74) and Figure 4 (Ridgway et al. *Ann Intern Med* 1972;77:549-55):

These observations are consistent with the pharmacological action that TSH secretion will decrease upon the rise in serum levothyroxine concentrations.

2.3.6 Does levothyroxine sodium injection prolong the QT or QTc interval?
This submission does not contain any QTc data for the assessment of QT prolongation.

2.4 Intrinsic Factors
2.4.1 What intrinsic factors may affect the use of levothyroxine sodium injection?
Pediatric
Levothyroxine sodium injection has very limited applicability to treat myxedema coma in all pediatric aged patients since the pathophysiology of the disease occurs primarily in the elderly population. However, the justification of pathophysiology may not hold true (b) (4) (b) (4)

PeRC (Pediatric Review Committee) recommended the following for levothyroxine sodium injection per the meeting on April 13, 2011:

- a full waiver for the sponsor to conduct pediatric study on the myxedema coma indication because the pathophysiology primarily occurs in the elderly population
- (b) (4)
- no Proposed Pediatric Study Request for pediatric PK study is necessary since the patient population will likely to be too small and levothyroxine dosing is titrated for safety

Geriatric
Myxedema coma occurs almost exclusively during or after the 6th decade with 80% of the cases occurring in women (C.G. Olsen's *J Am Board Fam Pract* 1995;8:376-83). Olsen recommended a loading dose of 250 – 500 µg (sic; mg in original text) levothyroxine for a 30 – 60 second intravenous administration and then follow with oral 100 – 170 µg (sic) daily maintenance dose. Elderly patients require a lower dose of levothyroxine since its degradation rate declines with aging.

Yamamoto et al. (*Thyroid* 1999;9:1167-75) also recommended elderly myxedema coma patients to be treated with low-dose levothyroxine.

2.4.2 What pharmacogenomic information is in the application?
This submission does not contain any pharmacogenomic data.

2.5 Extrinsic Factors
What are the potential drug-drug interactions for levothyroxine injection?
See the Labeling Comments section below for Section 12.3's drug interactions. Also, Surks and Sievert's review (*New Eng J Med* 1995;333:1688-94) contains the discussion on drug interactions with thyroid drugs.

2.6 Biopharmaceutics
What is the relative levothyroxine bioavailability upon intravenous and oral administration?
The sponsor cited the Maxon et al. article (*Int J Clin Pharmacol Ther Toxicol* 1983;21:379-82) to show the relative levothyroxine bioavailability between intravenous and oral administration in 21 healthy volunteers. Briefly, this was a parallel single-dose study with the following 4 treatments:

- IV SYNTHROID injection
- Oral solution (IV SYNTHROID injection)
- Oral SYNTHROID tablet
- Oral LEVOTHROID tablet

Maxon et al. used radioimmunoassay to quantitate serum levothyroxine concentrations. The relative oral bioavailability results follow (Table 9):

	Intravenous Injection as Reference	Oral Solution as Reference
Oral Solution	88%	-
LEVOTHROID Oral Tablet	72%	81.5%
SYNTHROID Oral Tablet	66%	74.5%

2.7 Bioanalytical
Are the bioanalytical methods properly validated for this NDA?
Not applicable since the sponsor did not conduct any clinical pharmacology study.

3. Labeling Comments
The yellow highlighted parts are Clinical Pharmacology's labeling recommendations.

18 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

S. W. JOHNNY W LAU
05/13/2011

SALLY Y CHOE
05/14/2011

CLINICAL PHARMACOLOGY
FILING CHECKLIST FOR NDA 20-2231

Applicant: APP Pharmaceuticals **Stamp Date: August 30, 2010**

NDA Number: 20-2231

Drug Name: Levothyroxine Sodium **NDA Type: Standard**

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			NA
2	Has the applicant provided metabolism and drug-drug interaction information?	X		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?			NA
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			NA
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			NA
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			NA
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			NA
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			NA
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			NA
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			NA
11	Is the appropriate pharmacokinetic information submitted?	Yes		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			NA
	General			

CLINICAL PHARMACOLOGY
FILING CHECKLIST FOR NDA 20-2231

13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	Yes		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	Yes		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	Yes		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes		
17	Was the translation from another language important or needed for publication?			NA

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

S. W. Johnny Lau, R.Ph., Ph.D.

Reviewing Pharmacologist Date

Sally Y. Choe, Ph.D.

Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY
FILING CHECKLIST FOR NDA 20-2231

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA	20-2231	Brand Name	To-be-determined
OCP Division	2	Generic Name	Levothyroxine sodium
Medical Division	DMEP, HFD-510	Drug Class	Thyroid hormone
OCP Reviewer	S.W. Johnny Lau	Indication(s)	Treat myxedema (b) (4)
OCP Team Leader	Sally Y. Choe	Dosage Form	Sterile lyophilized drug product for injection
Date of Submission	30-AUG-2010	Dosing Regimen	300 – 500 µg loading dose then 50 – 100 µg once daily maintenance dose
Estimated Due Date of OCP Review		Route of Administration	Intravenous
PDUFA Due Date		Sponsor	APP Pharmaceuticals
Division Due Date		Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Comments (Study number)
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
In vivo mass balance:				
In vitro isozyme characterization:				
In vitro metabolite Identity:				
In vitro metabolism inhibition:				
In vitro metabolism induction:				
In vitro mechanism of uptake in human liver				
In vitro plasma protein binding:				
Blood/plasma ratio:				
Pharmacokinetics (e.g., Phase I) -	X	1		Hays et al. J Clin Endocrinol Metab 51:1112-17 (1980)
Dose proportionality, healthy volunteers – fasting & non-fasting single and multiple doses:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
pediatrics:				
gender & geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:				
Phase 3:				
PK/PD:				
Phase 2, dose ranging studies:	X	4		Holvey et al. *Arch Intern Med* 113:89-96 (1964); Ridgway et al. *Ann Intern Med* 77:549-55 (1972); Arlot et al. *Intensive Care Med* 17:16-8 (1991); Ladenson et al. *Am J Med* 73:467-74 (1982)

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Phase 2				
Phase 3 clinical STUDIES (placebo controlled):				
Phase 3 clinical STUDIES (uncontrolled):				
Population Analyses -				
Meta-analysis:				
NONMEM:				
Population PK/PD analysis				
II. Biopharmaceutics				
Absolute bioavailability:	X	1		Maxon et al. *Int J Clin Pharmacol Ther Toxicol* 21:379-82 (1983)
Bioequivalence studies – traditional design				
Relative bioavailability	X	1		Blouin et al. *Clin Pharm* 8:588-92 (1989)
alternate formulation as reference:				
Food-drug interaction studies:				
Absorption site				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Phenotype studies:				
Chronopharmacodynamics				
Pediatric development plan				
Literature References				
QT prolongation assessment				
Total Number of Studies	X	7		

Fileability and QBR comments

	"X" if yes	Comments
Application fileable?	X	See Fileability discussion on the review's page 6.
Comments to be sent to firm?	X	We have noted that there is no drug exposure information of an approved levothyroxine injection product in your submission. If you have any information or data addressing this or any relative exposure information of your product comparing to that of an approved levothyroxine product (i.e., either injection product or oral tablet product), submit those information by December 20, 2010.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CLINICAL PHARMACOLOGY
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Filing Memo

CLINICAL PHARMACOLOGY	
NDA:	**20-2231**
Compound:	Levothyroxine sodium
Sponsor:	APP Pharmaceuticals
Submission Date:	August 30, 2010
Relevant PIND:	101,385
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background

This document presents to the review team the fileability of NDA 20-2231 from the clinical pharmacology perspective.

The FDA recently categorized levothyroxine sodium for injection a "Marketed Unapproved Drug," thus requiring an NDA submission and FDA approval in order to keep the product on the market. The sponsor received such a Warning Letter from the FDA on December 18, 2006. The sponsor reviewed the FDA Guidance for FDA Staff and Industry; Marketed Unapproved Drugs – Compliance Policy Guide, July 2006 and consulted the Unapproved Drug Decision Tree. Per that review and the available clinical and nonclinical data in the literature for the safety and efficacy of parenteral levothyroxine in the treatment of myxedema coma (b) (4) the sponsor submitted a 505(b)(2) NDA for their levothyroxine sodium injection product without any additional clinical studies for the indication of the treatment of myxedema coma, (b) (4) The sponsor had a pre-IND meeting for this product with the Division of Metabolism and Endocrinology Products (DMEP) on March 18, 2008.

Myxedema coma is a very rare disease.

Findings

- The sponsor did not reference any approved levothyroxine sodium product's findings of clinical pharmacology, efficacy, and safety information.
- No approved levothyroxine sodium injection exists in Drugs@FDA. The approved levothyroxine sodium products are oral tablets such as LEVO-T, LEVOLET, LEVOTHROID, LEVOTHYROXINE SODIUM, LEVOXYL, NOVOTHYROX, SYNTHROID, and UNITHROID as well as oral capsule as TIROSINT in Drugs@FDA.
- The sponsor did not conduct any clinical pharmacology study for their levothyroxine sodium injection product.
- Per the March 18, 2008 pre-IND meeting, DMEP recommended the sponsor to conduct a relative bioavailability study between the marketed oral levothyroxine tablets and the to-be-marketed intravenous levothyroxine injection in population as similar to myxedema coma patients as possible for the following reason:
    - To provide physicians more information in determining the appropriate dose for switching patients from IV to oral levothyroxine formulations or vice versa.
- Per the March 18, 2008 pre-IND meeting's post-meeting decision, the sponsor has the option of conducting single dose IV pharmacokinetic study with their levothyroxine sodium injection or providing data from literature. While a relative levothyroxine bioavailability study (oral tablets versus injection) will not be required for approval of the levothyroxine sodium injection, such study will provide useful information to prescribers. This recommendation is per the review of

distribution data for levothyroxine injection, which indicates significant use in a non-myxedema population.

- The sponsor cited 7 published clinical pharmacology studies and 2 textbook chapters to support the clinical pharmacology and biopharmaceutics information (see Attachment). The cited Maxon et al. study [*Int J Clin Pharmacol Ther Toxicol* **21**:379-82 (1983)] concerns the absolute levothyroxine bioavailability of oral tablets versus intravenous injection in young healthy men, and the absolute bioavailability is 0.66 and 0.72 for SYNTHROID® and LEVOTHROID®, respectively.
- The sponsor was uncertain whether any published studies used their levothyroxine sodium for injection. However, the formulation of the drug product should not affect the bioavailability of intravenous levothyroxine.
- The sponsor summarized several marketed bioanalytical assays with brief device descriptions and performance characteristics for measuring levothyroxine in human serum and heparinized plasma.
- The sponsor submitted proposed labeling with annotation. The cited studies' results and associated information seem to support the proposed labeling statements but this will be a review issue.
- Per the March 18, 2008 pre-IND meeting, DMEP requested the sponsor to justify a range of doses that are reasonable in different population of patients such as the elderly patients. The sponsor cited Holvey et al. Treatment of myxedema coma with intravenous injection. Arch *Intern Med* **113**:89096 (1964) to substantiate the dose rationale for the intravenous levothyroxine sodium. This will be a review issue.
- No data on the dose proportionality information of IV levothyroxine pharmacokinetics exists.
- This submission's review focus will be on the following:
    - proposed IV levothyroxine dose rationale
    - absolute bioavailability of levothyroxine
    - impact of the reformulation for all oral levothyroxine formulations on the assessment of levothyroxine absolute bioavailability
    - lack of dose proportionality of IV levothyroxine info
    - proposed labeling

Adequacy of Data for Review of the Proposed Labeling

As a cursory review for filing, the sponsor provided adequate published articles for substantive review of the proposed labeling. Briefly, the sponsor provided the following data in the proposed label:
Section 7:
DRUG INTERACTIONS: Summary of Clinical Pharmacology Studies and SYNTHROID® label
Section 8:
USES IN SPECIFIC POPULATION: Summary of Clinical Efficacy and Summary of Clinical Safety
Section 12:
CLINICAL PHARMACOLOGY:
12.1 Mechanism of Action: SYNTHROID® label
12.2 Pharmacodynamics: Summary of Clinical Efficacy and Summary of Clinical Safety
12.3 Pharmacokinetics: Summary of Clinical Pharmacology Studies

Fileability of NDA 20-2231

CLINICAL PHARMACOLOGY
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Per the Code of Federal Regulation (CFR) 320.1 "Requirements for submission of bioavailability and bioequivalence data"

(a) Any person submitting a full new drug application to the Food and Drug Administration (FDA) shall include in the application either:

(1) Evidence measuring the in vivo bioavailability of the drug product that is the subject of the application; or

(2) Information to permit FDA to waive the submission of evidence measuring in vivo bioavailability.

The sponsor does not have any in vivo bioavailability data and by submitting the literature data, (2) waiver option can be applied. Since this product is a parenteral solution intended solely for administration by injection, the following CFR applies on the waiver:

Sec. 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.

(b) For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration **as a drug product that is the subject of an approved full new drug application** or abbreviated new drug application.

The critical information that is missing for filing this NDA is the underlined portion of the last line above. Because there is no approved levothyroxine injection product to compare with, this waiver does not apply. Thus, the sponsor needs to conduct a pharmacokinetic study characterizing their bioavailability profile of their product to satisfy the CFR 320.21.

The sponsor did cite the Maxon et al. article to provide the relative bioavailability information between between Synthroid IV injection and Synthroid oral tablet as well as Levothroid oral tablet. The cited Maxon article could have provided the sponsor's levothyroxine sodium injection bioavailability information via linking the oral levothyroxine data. However, the NDA approval dates for Synthroid and Levothroid oral tablets are July 24, 2002 and October 24, 2002, respectively, per Drugs@FDA. Thus, Maxon studied unapproved Synthroid and Levothroid oral tablets before 1983. Had the sponsor studied any approved oral levothyroxine products, which may satisfy the waiver via linking the IV levothyroxine to an approved oral levothyroxine product(s).

The Sponsor, APP Pharmaceuticals, is currently the sole source of levothyroxine injection and therefore is supplying all IV levothyroxine demand. IV levothyroxine is determined to be a medically necessary drug.

Given this, it appears that from a filing perspective, the sponsor has submitted sufficient literature to conduct a review of IV levothyroxine bioavailability compared to an oral levothyroxine formulation. Balancing the need of the above issues, Clinical Pharmacology recommends filing this NDA and requests the sponsor to respond to the following:
"We have noted that there is no drug exposure information of an approved levothyroxine injection product in your submission. If you have any information or data addressing this or any relative exposure information of your product comparing to that of an approved levothyroxine product (i.e., either injection product or oral tablet product), submit those information by December 20, 2010."

Attachment starts here.

Study Ref No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Product ID)	Subject (No.)	C_{max} (µg/dL) Total T_4	T_{max} (hr)	AUC (µg·hr /mL)	C_{min} (µg/mL)	T ½ (d)	Other	Study Report Location
Maxon, 1983 (8)	To assess the absolute and relative bioavailability of two commercial L-thyroxine products	Open label, randomized, parallel, four arm study	182 µg, IV dose (mean dose for 5 subjects)	5 (dosed IV)	5.0 µg/dL (mean value for 5 subjects)	< 1 hr	46.8 µg·hr/dL (mean value for 5 subjects)	N/A	N/A	N/A	5.4
Blouin, 1989 (14)	To assess relative bioavailability of two L-thyroxine formulations	Open label, randomized BA study	100, 125, 150 and 200 µg Oral Levothroid & Synthroid	19	Levo 0.011 µg/dL ± 0.0017 Synth 0.011 µg/dL ± 0.0021	Levo 2.27 ± 0.83 Synth 2.56 ± 1.04	Levo µg·hr/dL 2338.5 ± 404.1 Synth µg·hr/dL 2169.9 ± 421.9	N/A	N/A		5.4

Study Ref No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Product ID)	Subject (No.)	C_{max} (µg/dL) Total T_4	T_{max} (hr)	AUC (µg·hr /mL)	C_{min} (µg/mL)	T ½ (d)	Other	Study Report Location
Ridgway, 1972 (10)	To assess the metabolic response in myxedema to IV L-thyroxine	Open label, two arm study	Group 1: 428 µg bolus IV then 100 µg daily IV x 9 days Group 2: 750 µg bolus IV then 200 µg daily IV x 9 days	14 (7 patients per group)	Group 1: 10 µg/dL post bolus Day 1 & 7.0 µg/dL after 10 days Group 2: 11.9 µg/dL post bolus Day 1 & 9.7 µg/dL after 10 days	< 1 hr	N/A	N/A	N/A	N/A	5.4
Arlot, 1991 (7)	Clinical response to oral and IV thyroxine in myxedema coma	Open label, 2 arm comparative study	IV: 1000 µg bolus followed by 500 µg on Day 6 and 12 Oral: 500 µg followed by 100 µg daily	7 female patients (2 patients IV, 5 patients PO)	IV: Patient 1: 18 µg/dL IV: Patient 2: 20 µg/dL	< 1 hr	N/A	N/A	N/A	N/A	5.4

Study Ref No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Product ID)	Subject (No.)	C_{max} (µg/dL) Total T_4	T_{max} (hr)	AUC (µg·hr /mL)	C_{min} (µg/mL)	T ½ (d)	Other	Study Report Location
Ladenson, 1982 (6)	Clinical response to IV thyroxine in primary hypothyroidism	Open label, single arm clinical response study	IV: 100 µg daily X 8 days	10 patients 9 Females 1 Male	5.5 µg/dL at 24 hours 6.2 µg/dL at end of 7 days	<1 hr	N/A	N/A	N/A	N/A	5.4
Hays, 1980 (15)	Distributional PK study of radiolabeled T_3 and T_4 administered IV and SC	Open label, distribution study	5 µCi ^{125}I labeled T_4 5 µCi ^{131}I labeled T_4	5 healthy subjects	N/A	N/A	N/A	N/A	4.97	N/A	5.4

Holvey et al. Treatment of Myxedema Coma with Intravenous Thyroxine. *Arch Intern Med* **113**:89-96 (1964). This article provides the dose rationale for intravenous levothyroxine sodium.

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/s/

S. W. JOHNNY W LAU
11/09/2010

SALLY Y CHOE
11/09/2010