CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 210632
Supporting document/s:	SDN1, SN0001
Applicant's letter date:	06/15/2018
CDER stamp date:	06/15/2018
Product:	Levothyroxine Sodium Injection
Indication:	For treatment of myxedema coma
Applicant:	Fresenius Kabi USA, Three Corporate Drive, Lake Zurich, IL, USA
Review Division:	Division of Metabolism and Endocrine Products
Reviewer:	Arulasanam K. Thilagar, PhD
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TABLE OF CONTENTS

Table of Tables

1 Executive Summary

1.1 Introduction

Fresenius Kabi USA (hereafter FK USA or the Applicant) seeks to market Levothyroxine Sodium Injection, a ready-to-use L-thyroxine (T4) formulation for the emergency treatment of myxedema coma, via the 505(b)(2) regulatory pathway. The Applicant conducted no nonclinical pharmacology or toxicology studies to support the safety of levothyroxine in Levothyroxine Sodium for Injection, but instead relies on the Agency's prior findings of safety and effectiveness for the listed drug (LD), a lyophilized levothyroxine sodium injection product marketed under NDA 202231 by FK USA. The Applicant also relies upon selected information available in the public literature. The LD is approved for the emergency treatment of myxedema coma, but it must be reconstituted prior to intravenous administration. The ready-to-use Levothyroxine Sodium Injection formulation specified in this NDA has the same active pharmaceutical ingredient (API) as the lyophilized LD. The proposed indication for the treatment of myxedema coma is identical to the LD. Like the LD, the initial intravenous loading dose of Levothyroxine Sodium Injection is between 300 and 500 mcg followed by once daily intravenous maintenance doses between 50 and 100 mcg as clinically indicated, until the patient can tolerate oral therapy.

1.2 Brief Discussion of Nonclinical Findings

Potential adverse effects related to levothyroxine treatment are associated with excess circulating thyroid hormone, which is clinically manageable. Indeed, the toxicity of levothyroxine in euthyroid animals is directly related to the expected exaggerated pharmacology of levothyroxine, i.e., drug-induced hyperthyroidism. Therefore, it is reasonable to rely on finding of safety of the LD for the safety qualification of the levothyroxine active pharmaceutical ingredient (API). However, other characteristics of Levothyroxine Sodium Injection are different from that of the LD, including amounts of degradants, types of excipients, product-specific impurities, and container closure system leachables. Therefore, this safety review will focus on these significant differences between Levothyroxine Sodium Injection and the LD. Recommended product labeling will also be addressed.

Degradants

Two degradation products, liothyronine (T3) and 3,5-diiodo-L-tyrosine (DIT) were identified as degradants of concern. The overall level of degradation products specified for the Applicant's Levothyroxine Sodium Injection drug product is (b) (4)%, which is (b) (4)% higher than levels specified for the LD ((b) (4)%), which is primarily due to higher levels of T3 and DIT. However, both T3 and DIT are endogenous compounds. The toxicity of the active T3 hormone is well documented, and therefore T3 is considered qualified from a nonclinical point of view. DIT is an endogenous inactive precursor of levothyroxine and therefore also considered qualified.

Excipients
The proposed Levothyroxine Sodium Injection product has tromethamine, sodium iodide and sodium chloride, whereas the LD does not. The excipients in Levothyroxine Sodium Injection are present in concentrations below the Agency's Inactive Ingredients Database (IID) limits for the intravenous route of administration and are therefore not a safety concern.

Impurities
Levothyroxine Sodium Injection Finished Product complies with the requirements of ICH Q3D Guideline for elemental impurities. No other impurity concerns were noted.

Leachables
The levels of leachable compounds present in the drug product (based on the maximum dose) at expiry were at acceptable levels.

Labeling - Reproduction, and Mutagenicity, Carcinogenicity and Fertility
The levothyroxine drug substance in Levothyroxine Sodium Injection is chemically identical to endogenous human T4. Animal studies have not been performed to evaluate reproduction, mutagenic or carcinogenic potential, or effects on fertility of levothyroxine.

1.3 Recommendations

1.3.1 Approvability

This NDA is approvable from a Pharm/Tox perspective.

1.3.2 Additional Nonclinical Comments

None.

Reviewer Recommended Labeling:

This reviewer agrees with the nonclinical portion of Applicant's label (see the Appendix).

2 Drug

2.1 Drug Identity

Name
Levothyroxine Sodium Injection

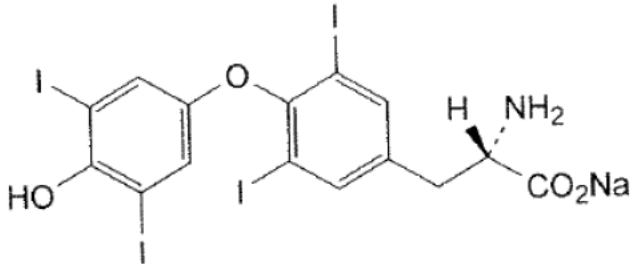
Chemical Name:
L-tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodomonosodium salt, hydrate

CAS Registry Number
CAS No. [55-03-8]

Generic Name
L-thyroxine sodium

Molecular Formula/Molecular Weight
$C_{15}H_{10}I_4NNaO_4$/798.85 g/mol

Structure or Biochemical Description



Pharmacologic Class
L-thyroxine (T4)

Manufacturer of API
(b) (4)

Manufacturer of Drug Product
FK USA
2020 North Ruby Street
Melrose Park, IL 60160

The following Letters of Authorization provided by the Applicant are presented in the Appendix of this Review.

1. The letter from (b) (4), permitting FDA to cross-reference DMF (b) (4) on behalf of FK USA.
2. DMF authorization letter from the vial manufacturer (b) (4) DMF (b) (4).
3. DMF authorization letters from the stopper manufacturers, (b) (4), DMF's (b) (4) and (b) (4).
4. DMF authorization letter from the drug product manufacturer, FK USA, DMF (b) (4).

The following Statements of Right of Reference provided by the Applicant are presented in the Appendix of this Review.

1. Letter of Authorization, DMF Type II (b) (4), Levothyroxine Sodium
2. Letter of authorization, Entire Content of DMF (b) (4)
3. Letter to authorize FK USA to incorporate by reference information regarding (b) (4) in Master File DMF (b) (4)
4. Letter to authorize FK USA to incorporate by reference information regarding (b) (4) in Master File DMF (b) (4)

2.2 Reference Drug

Levothyroxine Sodium Injection (NDA 202231)

2.3 Relevant INDs, NDAs, BLAs and DMFs

DMF (b) (4)
DMF (b) (4)
DMFs (b) (4)
DMF (b) (4): FK USA (drug product manufacturing)
NDA 202231: FK USA (LD)

2.4 Drug Formulation

The drug product is provided as 100 µg/5mL, 200 µg/5mL and 500 µg/5mL. The components and composition of the final drug product and the function of each excipient are given below.

Table 1: Component Composition per Unit Dose for Product Code 885110

Packaging Configuration	5 mL fill in a 10 mL vial			
Strength	100 mcg / 5 mL			
Concentration	0.02 mg/mL			
Vial	10 cc, (b) (4) Glass vial			
Stopper	(b) (4)			
Seal	(b) (4) seal			
Ingredient	**Content per mL**	**Content per 5 mL (unit)**	**Function**	**Quality of Ingredient**
Levothyroxine Sodium	20 mcg	100 mcg	Active Ingredient	USP
Tromethamine	10 mg	50 mg	(b) (4)	USP
Sodium Iodide	0.14 mg	0.7 mg		USP
Sodium Chloride	6.48 mg	32.4 mg		USP
(b) (4)				
Hydrochloric Acid, (b) (4) / Sodium Hydroxide, NF	As required	As required	pH Adjuster	NF

Table provided by the Applicant

Table 2: Component Composition per Unit Dose for Product Code 887110

Packaging Configuration	5 mL fill in a 10 mL vial			
Strength	200 mcg / 5 mL			
Concentration	0.04 mg/mL			
Vial	10 cc, (b) (4) Glass vial			
Stopper	(b) (4)			
Seal	(b) (4) seal			
Ingredient	**Content per mL**	**Content per 5 mL (unit)**	**Function**	**Quality of Ingredient**
Levothyroxine Sodium	40 mcg	200 mcg	Active Ingredient	USP
Tromethamine	10 mg	50 mg	(b) (4)	USP
Sodium Iodide	0.14 mg	0.7 mg		USP
Sodium Chloride	6.48 mg	32.4 mg		USP
(b) (4)				
Hydrochloric Acid, (b) (4) / Sodium Hydroxide, NF	As required	As required	pH Adjuster	NF

Table provided by the Applicant

Table 3: Component Composition per Unit Dose for Product Code 887110

Packaging Configuration	5 mL fill in a 10 mL vial			
Strength	500 mcg/ 5 mL			
Concentration	0.1 mg/mL			
Vial	10 cc, (b) (4) Glass vial			
Stopper	(b) (4)			
Seal	(b) (4) seal			
Ingredient	**Content per mL**	**Content per 5 mL (unit)**	**Function**	**Quality of Ingredient**
Levothyroxine Sodium	100 mg	500 mcg	Active Ingredient	USP
Tromethamine	10 mg	50 mg	(b) (4)	USP
Sodium Iodide	0.14 mg	0.7 mg		USP
Sodium Chloride	6.48 mg	32.4 mg		USP
(b) (4)				
Hydrochloric Acid, (b) (4) / Sodium Hydroxide, NF	As required	Q.S. to volume	pH Adjuster	NF

Table provided by the Applicant

Table 4: Formulation Comparison between RLD and Proposed Drug:

	Reference Listed Drug	Proposed Drug Product
Name	Levothyroxine Sodium for Injection (Fresenius Kabi USA, LLC)	Levothyroxine Sodium Injection
Conditions of Use (Indications)	Indicated for the treatment of myxedema coma	Indicated for the treatment of myxedema coma
Dosage Form	Lyophilized Powder	Solution
Route of Administration	intravenous	intravenous
Active Ingredient	Levothyroxine Sodium, USP	Levothyroxine Sodium, USP

Table provided by the Applicant

Table 5: Formulation Comparison between RLD and Proposed Drug (Cont.)

	Reference Listed Drug	Proposed Drug Product
Strength	20, 40, 100 mcg/mL	20, 40, 100 mcg/mL
	Excipients (amount/mL)	
	Sodium Phosphate, USP (b) (4)	Tromethamine, USP 10 mg
	Mannitol, USP (b) (4)	Sodium Iodide, USP 0.14 mg
	(b) (4)	Sodium Chloride, USP 6.48 mg
		(b) (4)
		(b) (4)
Hydrochloric Acid, NF	(b) (4)	As required to adjust pH
Sodium Hydroxide, NF		As required to adjust pH

Table provided by the Applicant

2.4.1 Excipients

Table 6: Inactive Ingredients Amounts per IID

Fresenius Kabi USA, LLC (FK USA)'s Excipients	Amount per Unit	IIG Levels
Tromethamine	1% (10 mg/mL)	1.2%
Sodium Iodide	0.014% (0.14 mg/mL)	1%
Sodium Chloride	0.648% (6.48 mg/mL)	0.9%

Table provided by the Applicant

All inactive ingredients used in the formulation of the proposed drug product comply with the current compendia and are within their IID limits.

2.4.2 Residual Solvents

Drug Substance, Levothyroxine Sodium, USP raw material specifications comply with the residual solvents' limits per ICH Q3C.

- (b) (4) is used in the manufacturing process of Levothyroxine Sodium, USP. The proposed limit of NMT (b) (4) ppm is tighter then the Class 3 ICH Q3C requirement of 3000 ppm
- (b) (4) is used in the manufacturing process of Levothyroxine Sodium, USP. The proposed limit of NMT (b) (4) ppm is tighter then the Class 3 ICH Q3C requirement of 5000 ppm.

- (b) (4) is used in the manufacturing process of Levothyroxine Sodium, USP. The proposed limit of NMT (b) (4) ppm complies with the Class 3 ICH Q3C requirement of 5000 ppm.

(b) (4) is used in the manufacturing process of Levothyroxine Sodium, USP. The proposed limit of NMT (b) (4) ppm complies with the Class 3 ICH Q3C requirement of 5000 ppm. The Levothyroxine Sodium Injection drug product formulation contains Levothyroxine Sodium USP, Sodium Chloride USP, Tromethamine USP, Sodium Iodide USP, and Water for Injection. Sodium Chloride USP, Sodium Iodide USP and Tromethamine USP do not contain solvents, including those established per USP<467> as Class 1, 2 or 3 solvents or other solvents per the supplier certifications (10-07-01-0061, 10-07-01-0166A and 10-07-01-0311).

2.5 Container Closure System (Levothyroxine Sodium, USP, (b) (4))

Levothyroxine Sodium Injection is (b) (4) .

The following DMF Authorization letters from the vial and stopper manufacturers are provided in this NDA and are presented in the Application.

- (b) (4), DMF (b) (4) letter.
- (b) (4), DMF (b) (4) and DMF (b) (4) letters.

2.5.1 Leachables

FK USA performed a leachable simulation study for the assessment by using extraction conditions which accelerate the product use conditions. The simulated leachable study is performed under accelerated temperature conditions using the finished drug product (formulation, container closure system, product fill volume, and product/component sterilization conditions).

Levothyroxine Sodium Injection is indicated for treatment of myxedema coma. It may be administered as a loading dose of 300-500 µg intravenously on the first day, followed by a maintenance dose between 50-100 µg/day until the patient can tolerate oral therapy. The maximum daily dose (MDD) is 500 µg. Transfer from injectable administration to oral administration occurs within 30 days, so the dose duration can be categorized as acute, less than 30 days.

Identities and amounts of volatile compounds, semi volatile compounds and extracted compounds and the ratio PDE/human dose is provided in Tables 7, 8, and 9.

Extractable Studies of the (b) (4) Stopper

The Applicant used HS GC/MS, GC/MS, UHPLC/UV/MS and ICP/MS techniques to analyze the volatile, semi-volatile, non-volatile extractable compounds. The results are presented in the following Tables. The amounts found are not of toxicological concern.

Table 7: Semi-Quantitative Estimates of Volatile Compounds by HS GC-MS Analysis of The (b) (4) Stopper (Study #1)

Extractable	CAS Number	amount (µg /stopper)[1]	Permissible Daily Exposure (PDE) for Solvent Residues[3], other reference[4, 5]	Ratio PDE/human dose[2]
(b) (4)			Class 3, up to (b) (4) mg/day.	(b) (4)
			Compound is not a scheduled solvent in Q3C(R5), but is a related structural analog of (b) (4) which is Class 2 with estimated PDE (b) (4) mg/day.	
			Compound is not a scheduled solvent in Q3C(R5), but is a related structural analog of (b) (4) which is Class 2 with estimated PDE (b) (4) mg/day.	
			Class 2, (b) (4) mg/day.	
			Compound is not a scheduled solvent in Q3C(R5), but is a related structural analog of (b) (4) which is Class 2 with estimated PDE (b) (4) mg/day	
			Class 2 solvent, (b) (4) mg/day[3]	
			TE = (b) (4) mg/day (adult) TE = (b) (4) mg/day (neonate)[6]	
			(b) (4) µg /kg/day, mg/day for a 50 kg human[4].	
			TE = (b) (4) mg/day (adult) TE = (b) (4) mg/day (neonate)[5]	

2 Ratio PDE/human dose = PDE / [(amount/stopper) x (500 µg levothyroxine day) x (1 vial / 100 µg levothyroxine)]
Table provided by the Applicant

Table 8: Semi-Quantitative Estimates of Semi-Volatile Compounds Detected by GC-MS Analysis of the 65% Ethanol/35% Water Extract of (b) (4) Stopper (Study #1)

Extractable	CAS Number	Conc.(µg/stopper)	TE (µg/kg/d)	Margin of Safety[1]
(b) (4)				

1 MOS = (TEi.v. x 50 kg) / [(µg/stopper) x (500 µg levothyroxine/day) x (1 vial/100 µg levothyroxine)]
Table provided by the Applicant

Table 9: Semi-Quantitative Estimates of Extractable Compounds Detected by HPLC/UV/MS Analysis of the 65% Ethanol /35% Water Extract of (b) (4) Stopper (Study #1).

Extractable[1]	CAS Number	Conc.(µg/stopper)[1]	TE (µg/kg/d)[2]	Margin of Safety
(b) (4)				

MOS = (TEi.v. x 50 kg) / [(µg/stopper) x (500 mg levothyroxine/day) x (1 vial/100 mg levothyroxine)]
Table provided by the Applicant

Only (b) (4) was detected above the TTC, but with a high margin of safety ((b) (4)), as shown in **Table 9.**

Table 10: Semi-Quantitative Estimates of Semi-Volatile Compounds Detected by GC-MS Analysis of the pH 2.5 Aqueous Solution Extract of (b) (4) Stopper (Study #2)

Extractable	CAS Number	Conc.(µg/stopper)
(b) (4)		

Table provided by the Applicant

Only (b) (4) was detected, but at a level below the threshold of toxicological concern (TTC = (b) (4) µg/stopper), as shown in **Table 10.**

2.5.2 Inorganic Compounds

Levothyroxine Sodium Injection is stored at "room temperature" for up to (b) (4) months in its commercial form. However, the extraction temperature of 55°C was chosen to accelerate the migration of leachable compounds from commercial container materials (vial and stopper) into the drug product formulation (simulation study). Duration of incubation at 55°C was 14 days.

(b) (4) were observed at marginally greater concentration in the Test Article extract than in the Levothyroxine Control blank (Table 8). The marginal amounts observed in the test article extracts were orders of magnitude below a calculated permissible daily exposure (PDE), and therefore there is no human dosing toxicological

concern for leachable elements that may migrate from these container materials (vial and stopper).

Table 11: Quantitative Estimates of Elements Detected by ICP/MS Analysis in Levothyroxine Sodium Injection solution formulation in vial with (b) (4) stopper (reference 4) stored at 55°C for 14 days.

Extractable Element	Conc. in levothyroxine Blank Control (ng/mL)	Total conc. in Test Article (ng/mL)	Conc. contributed solely by container (ng/mL)	Total amount per vial (ng/vial)	Total Human Daily Exposure (ng/day)	Permissible daily exposure[B-G] (µg/d)	Margin of Safety[A]
(b) (4)							

* This is a common element and is considered with less toxicity and not included in ICH Q3D and USP <232> for monitoring. Use the highest PDE number in ICH Q3D Target Class 3 element (b) (4) for setting up the PDE.
A Total amount per vial = total conc. in test article x 5 mL/vial
Human Daily Exposure (ng/day) = (total amount/vial) x (5 vials/day)
Margin of Safety = PDE (or TE) / (human daily exposure)
B Reference 9, 10, 11 USP <232> & ICH Q3D Elemental Impurities.
C Reference 12 (b) (4)
D Reference 13 (b) (4)
E Reference 15 (b) (4)
F Reference 17 (b) (4);
G Reference 16 (b) (4)
Table provided by the Applicant

2.5.3 Organic Leachable Compounds

No volatile organic compound previously identified ((b) (4)), which were observed previously in the extractable study of the stopper material, were not detected as volatile leachable compounds in this leachable study of the container/closure system using the Levothyroxine Sodium Injection formulation. Based on this, it is recommended that no organic or inorganic leachables need to be monitored for accumulation during subsequent Levothyroxine Sodium Injection product stability studies.

2.5.4 Elemental Impurities

Elemental impurities of concern for parenteral drug products, including (b) (4), pose no risk for use of Levothyroxine Sodium Injection, because the product complies with the requirements of ICH Q3D (1) guideline for elemental impurities.

2.5.5 Degradation Products

The Applicant proposed specification limits for degradation products based on specifications described in ICH guidelines Q3B(R2). Two degradation products, (b) (4) and (b) (4) were identified that exceed those thresholds.

Table 12: Degradation Products

Chemical Name	Code #	MDD	QT (%)	QT (TDI) (µg) (%)	Regulatory QT Threshold (%)	Proposed AC for Specified Degradation Product	Justification if proposed AC (%) > Regulatory QT Threshold (%)
(b) (4)							

Table provided by the Applicant

Degradation Product: Liothyronine (T3)

T3 is the primary active metabolite of levothyroxine. Levothyroxine is converted to T3 by deiodination. Levels of liothyronine are controlled at NMT (b) (4) % in the drug substance and a limit of NMT (b) (4) % is proposed for the finished product. This limit is same as that for LD (FK USA's Levothyroxine Sodium for Injection, NDA 202231).

During development, T3 was seen to increase due to light exposure, decreased pH and increase temperature, as these conditions favor the deiodination process; however, it did not increase significantly during storage. Based on the statistical analysis of available exhibit batch data and as qualified by LD, the limit of NMT (b) (4) % proposed for T3 degradant is acceptable.

Degradation Product: 3,5-Diiodo-L-Tyrosine (DIT)

The level of DIT is higher than the identification and qualification thresholds (NMT (b) (4) %). DIT is a precursor molecule in the synthesis of T4 in the thyroid gland and is chemically indistinguishable from the endogenous precursor to T4.

The proposed limit for DIT is based on the nine exhibit batches. The level of DIT has been qualified toxicologically to support a limit of (b) (4) % ((b) (4) µg/day) by the Applicant. Two different *in silica* (Q)SAR systems (OECD Toolbox version 3.3.0.132 and ToxTree version 2.6.6) predicted no mutagenic potential for DIT. In addition, DIT is also regarded as a metabolite of levothyroxine and therefore, it is qualified based on ICHQ3B(R) (13).

The proposed label recommends the maximum daily dose (MDD) of 500 mcg of Levothyroxine Sodium. The amount of DIT in the MDD would be (b) (4) % x500 mcg = (b) (4))

Proposed limit for any unspecified degradation product in Levothyroxine Sodium Injection (b) (4) the ICH threshold for identification and qualification which is NMT 1.0%.

Table 3.2.P.5.6- 6 Justification of Unspecified Degradation Products

MDD	IT (%)	IT (TDI) (µg) (%)	Regulatory IT Threshold (%)	Proposed AC (%)	Not acceptable if proposed AC (%) > Regulatory IT Threshold (%)
500µg	1.0%	5µg (1.0%)	1.0%	(b) (4) %	(b) (4)

Table provided by the Applicant

3 Description of Dosage Form

Levothyroxine Sodium Injection is supplied as a solution for injection at three strengths in single dose clear glass vials: 100 mcg per 5 mL (20 mcg per mL), 200 mcg per 5 mL (40 mcg per mL), and 500 mcg per 5 mL (100 mcg per mL).

4 Proposed Clinical Population and Dosing Regimen

Levothyroxine Sodium Injection is indicated for the treatment of myxedema coma. Important Limitations of Use: An initial intravenous loading dose of Levothyroxine Sodium Injection between 300 to 500 mcg followed by once daily intravenous maintenance doses between 50 and 100 mcg, as clinically indicated, is administered until the patient can tolerate oral therapy.

5 Regulatory Background

This NDA is submitted by FK USA via the 505(b)(2) pathway. The LD is Levothyroxine Sodium for Injection (NDA (b) (4)), also manufactured by FK USA. Reference is made to the FK USA IND application for Levothyroxine Sodium Injection that included an initial pediatric study plan submitted on 29 June 2017 (the Agreed Upon Initial Pediatric Study Plan is dated December 1, 2017).

6 Nonclinical Studies

6.1 Studies Submitted

No nonclinical studies have been conducted by the Applicant. The Applicant intends to rely on the FDA's previous findings of safety and efficacy data contained in the approved NDA 202231 and the published literature to support its 505(b)(2) submission. The route of administration and dosing regimen (dose, frequency, and duration) for the Applicant's premixed liquid Levothyroxine Sodium Injection will be same as the diluted LD (20).

The Applicant performed literature searches to provide documentation for the nonclinical pharmacology, pharmacokinetics and toxicology of levothyroxine. The literature searches were performed using the following separate databases:

- Medline – this database is managed by the National Library of Medicine and contains citations from 1950 to the present.

- Toxnet – this resource is a cluster of databases covering toxicology, hazardous chemicals, environmental health and related areas and is managed by the National Library of Medicine. Toxnet contains citations from 1965 to the present. Searches in these databases, were performed on 23 July 2009. The searches were updated on 11 April 2018 from Embase database.

The literature referenced studies do not have references to GLP compliance and therefore are considered non-GLP studies. In addition, the routes of administrations of the drug are different from the proposed clinical route. Toxicokinetic information is not provided in these studies. In view of this, the scientific value of the information provided in the literature for human safety is limited.

6.2 Pharmacology

6.2.1 Mode of Action

Endogenous levothyroxine (T4) is produced solely by the thyroid gland. Approximately 80-100 µg of T4 is produced daily. Most of triiodothyronine (T3) is derived from peripheral deiodination of T4 to T3, primarily in the liver and kidneys. The total daily production rate of T3 is 30-40 µg **(21)**.

Thyroid hormone synthesis and secretion is tightly regulated by the hypothalamic-pituitary- thyroid axis. Thyrotropin-releasing hormone (TRH) released from the hypothalamus stimulates secretion of thyrotropin-stimulating hormone (TSH), from the anterior pituitary gland. TSH, in turn, is the physiologic stimulus for the synthesis and secretion of thyroid hormones, L-thyroxine (T4) and L-triiodothyronine (T3), by the thyroid gland. Circulating serum T3 and T4 levels exert a feedback effect on both TRH and TSH secretion **(22)**.

Thyroid hormones are the main controllers of the basal metabolic rate and accelerate the rate of cellular oxidation increasing the uptake of oxygen by the mitochondria, the efficiency of oxidative phosphorylation and Na/K-dependent ATPase Thyroid hormones also stimulate gluconeogenesis and protein synthesis and play a role in the synthesis and degradation of lipids.

Thyroid hormones play a role in growth and development. When T4 gets into the cell and is converted to T3 by 5'-deiodinase activities. T3 then enters the nucleus where it binds

to a specific receptor. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins (**22, 23**).

Thyroid hormones are required for normal maturation of bone and the central nervous system. Mental retardation is a consequence of thyroid hormone deficiency. Thyroid hormone is required for maturation and normal structural formation of the epiphyses. In children, thyroid hormone deficiency leads to epiphyseal dysplasia and delayed bone age. In adults, thyroid hormone directly stimulates osteoclasts to enhance bone resorption. Thyroid hormone excess may result in decreased bone mineral content and osteopenia **(22, 23).**

Thyroid hormones stimulatory effect on the myocardium, result in increased heart rate, cardiac contractility and cardiac output. This could be due to either a direct stimulatory action of hormone on myocardial membrane Ca+2-ATPase activity, or a direct effect of hormone to increase the number of β-adrenergic receptors, thereby enhancing sensitivity of the myocardium to the effects of catecholamines. Excess of thyroid hormone include arrhythmias, angina, congestive heart failure, and infarction **(20)**.

6.2.2 Nonclinical Pharmacology

Levothyroxine sodium for injection acts like the endogenous T4 produced naturally in the thyroid gland. Thyroid hormone primarily functions to increase metabolism (i.e., protein synthesis), growth and development (i.e., growth hormone, bone growth, and neuronal maturation), and catecholamine effect (i.e., adrenaline The animal toxicity of Levothyroxine is mostly related to expected exaggerated levothyroxine pharmacology (i.e., hyperthyroidism – weight loss, increased food consumption, increased heart rate, increased blood pressure) in thyroid-status compromised or uncompromised animals (i.e. mice, rats, guinea pigs, rabbits, or dogs) via different routes (i.e., intraperitoneal, subcutaneous, oral, or intravenous). Some CNS (i.e., changes in amygdale-related behavior in adult, spatial learning, and hippocampal morphology) and CV findings (i.e., cardiac hypertrophy) were linked with levothyroxine in animals.

The nonclinical pharmacologic profile of Levothyroxine Sodium, USP is well-characterized **(21)**. Intraperitoneal (i.p.) administration of levothyroxine to rats for 14 days induced evidence of hyperthyroidism such as weight loss, elevation of rectal temperature, increased heart rate and oxygen consumption **(24)**. SC administration of levothyroxine to rats for 3 weeks resulted in an increase in food and water intake, body temperature, heart rate, systolic blood pressure, and serum T3, T4 and triglyceride levels **(25)**. Hyperthyroidism was also induced in guinea pigs with normal uncompromised thyroid status and hormonal homeostasis by daily i.p. injection of levothyroxine for 7 days and resulted in the manifestation of weight loss, increased heart rate, loss of hair and increased levels of T4 **(26)**.

Suppression of thyroid and pituitary function was evident after administration of a replacement dose of levothyroxine to euthyroid dogs **(27)**. In addition, the effects of long-term thyroxine treatment were determined on the pituitary and thyroid glands of healthy

dogs. The activity of the thyroid gland was decreased in healthy dogs during thyroxine treatment, as indicated by decreases in epithelial volume density, epithelial height and follicular area and increases in colloid volume density, compared with thyroid gland activity in nontreated dogs (**28)**.

The glomerular filtration rate (GFR) **(29)**, tissue oxygenation **(30)**, oxidative stress **(31, 32)**, lipid metabolism and plasminogen activator (PA) activity **(33)** are modulated by T4 levels

Applicant's literature search did not reveal standard, Good Laboratory Practices (GLP) safety pharmacology evaluations of levothyroxine for the cardiovascular, neurological, respiratory or gastrointestinal systems. However, the literature provided information on the effects of levothyroxine on cardiovascular function and the central nervous system (CNS) investigation and characterization in nonclinical studies. The CNS effects of juvenile-onset hypothyroidism on the number of distribution of spines along with pical shaft of pyramidal neurons of the visual cortex, appeared to be potentially reversible with adequate thyroxine (T4) therapy (**34**). The degree of restoration appeared related to the concentration of T3.

Levothyroxine-induced cardiac hypertrophy is associated with arrhythmias, including prolonged QT interval in rats **(35)**. Evidence indicate that the adrenergic system may impart a significant role in arrhythmias associated with hyperthyroidism **(37)**. Repeated administration of levothyroxine has been shown to alter cardiac protein biosynthesis and metabolic activities associated with hypertrophy and altered functionality in rats (**26**). The capacity of levothyroxine to induce cardiac hypertrophy was studied in rats **(38)**. Levothyroxine showed a small effect on mean blood pressure, a larger effect on heart rate, and caused a large increase in cardiac output. However, Sprague Dawley rats treated with levothyroxine showed increased heart weight, left ventricular systolic pressure and dP/dT **(39)**. In thyroxine treated rats with cardiac hypertrophy, Angiotensin II levels and Angiotensin II type 2 receptor expression was significantly increased **(40)**. In levothyroxine-treated Sprague Dawley rats, cardiomyocytes showed decreased contractility and increased susceptibility to apoptosis **(41)**. When L-thyroxine and D-thyroxine were administered i.p. to Wistar rats they induced an inhibition of glucose-induced insulin secretion with comparable time-and dose-dependent characteristics. L-thyroxine was ten times more potent than D-thyroxine. The prominent effect of L-thyroxine was the inhibition of the late phase of glucose-induced insulin secretion. **(42**).

In rats, neonatal hyperthyroidism induced persistent alterations in the brains of adult rats associated with behavioral changes **(43)**.

6.2.3 Pharmacokinetics

Absorption

Applicant obtained absorption data from three articles, in which levothyroxine (T4) in which the dogs were administered levothyroxine orally. Overall, time to maximum

concentration (t_{max}) ranged from 3 to approximately 7 hours and was similar with tablet and solution oral formulations. Half-life ($t_{1/2}$) ranged from 8.6 to 14.6 hours.

Distribution
Applicant presented distribution (placental transfer) data from one article in which the pregnant rats were administered levothyroxine through a jugular cannula. The minimal placental transfer of T4 occurs in the rat during the last days of gestation, and the amount of T4 transferred to the fetus is minimal compared to the quantity of T4 secreted by the fetal thyroid at this stage of development.

Metabolism
Applicant presented nonclinical levothyroxine metabolism and excretion obtained from one article performed with isolated perfused rat livers and in rats with biliary fistulas. When sodium salicylate was added to the perfusing blood containing T4- 131^{I}, a progressive increase in the rate of disappearance of the T4 from the blood and an increased uptake of T4 by the isolated liver were observed. The biliary output of 131^{I} was much greater than in untreated rats. The urinary output of 131^{I} was somewhat higher when salicylate was administered in untreated rats. Increased rates of conjugation of T4 with glucuronic acid and excretion of the T4 glucuronide in bile occurred with the 12.5-mg dose of salicylate. Deiodination of the hormone in the liver was depressed with the higher doses of salicylate.

Clearance
One referenced article describes the hepatobiliary clearance of T4, by Hepatic microsomal enzyme induction and increased glucuronidation of T4 enhance hepatobiliary clearance using Wistar rats **(2)**. It was shown approximately 3% of the total administered dose of [125^{I}] T4 was excreted into bile over the collection interval in Wistar rats.

Most of thyroxine metabolism in humans occurs in the liver and can be deiodinative or non-deiodinative. Deiodinative metabolism consists of sequential monodeiodination to triiodothyronine T3 or reverse T3, which is further deiodinated to monoiodothyronine, which is an inactive normal plasma constituent **(3)**. Thyroxine may also be conjugated with glucuronic and sulfuric acids through the phenolic hydroxyl group and excreted in the bile or released via hydrolysis of the conjugates in the intestines and reabsorbed. Some reaches the colon unchanged where it is hydrolyzed and eliminated in the feces as the free compound **(3)**.

Applicant presented information from eight studies from the nonclinical literature on the pharmacokinetics of Levothyroxine.

Table 2.6.4-1 Pharmacokinetics Program for Levothyroxine

Reference (Study Number)	Study Type and Duration	Route of Administration	Species	GLP (yes/no)
La Traon, et al. 2008 (4)	Bioavailability study, single dose and repeat dose	Oral and i.v.	Dogs	Unknown (published literature)
Nachreiner et al. 1993 (5)	Bioavailability study, single and divided dose	Oral	Dogs	Unknown (published literature)
Wood, et al 1990 (6)	Bioavailability study, single dose	Oral	Dogs	Unknown (published literature)
Dussault and Coulombe, 1980 (7)	Distribution (placental transfer), 3 days	i.v.	Rats	Unknown (published literature)
Lecureux, et al 2009 (2)	Excretion, 4 days	i.v.	Rats	Unknown (published literature)
Flock and Owen, 1965 (8)	Drug Interaction, 24 hours	i.v.	Rats	Unknown (published literature)
Jin, et al, 2005 (9)	Drug Interaction, 3 weeks	Oral	Rats	Unknown (published literature)
Phillips, et al, 1974 (10)	Drug Interaction, single dose	Gavage	Rats	Unknown (published literature)

i.v. = Intravenous; GLP = Good Laboratory Practices
Table provided by the Applicant

The Applicant provided their nonclinical data based on their literature searches using Medline, and Toxnet.). The information to support the pharmacokinetic profile of Levothyroxine sodium for injection were based on non-GLP studies and are presented in the following Tabulated summaries.

6.3 Drug -Drug Interaction

Interactions between thyroid hormone and many drugs are documented. These interactions are known to affect the therapeutic responses of Levothyroxine Sodium Injection and the interacting drugs. Leothyroxine interaction with antidiabetic agents or insulin, oral anticoagulant therapy, digitalis glycosides and antidepressive agents, (e.g., amitriptyline) or tetracyclic (e.g., maprotiline), Ketamine, Sympathomimetics and other drugs are documented in the drug label.

Applicant presented information from eight studies from the nonclinical literature on the pharmacokinetics of Levothyroxine.

Applicant presented information from three articles from the literature to report nonclinical drug-drug interactions in rat models. Sodium salicylate increased the uptake of levothyroxine in the liver, increased biliary and urinary output of 131^{I} and increased rates of conjugation of levothyroxine with glucuronic acid. Coadministration of oral colestipol

hydrochloride and levothyroxine resulted in a decreased absorption of levothyroxine. In addition, oral administration of levothyroxine can induce Pglycoprotein in the duodenum. When levothyroxine is administered in combination with cyclosporine A, the absorption of cyclosporine A, which occurs mainly from the upper intestine, is reduced as a result of efflux transport via P-glycoprotein induced by levothyroxine.

Pharmacokinetic nonclinical drug-drug interactions studies in rats are very limited **(8).** In these studies, interactions occurred between levothyroxine and sodium salicylate (increased metabolism and excretion of levothyroxine), colestipol hydrochloride (decreased absorption of levothyroxine) and cyclosporine A (reduced absorption of cyclosporine A due to levothyroxine induction of P-glycoprotein). In humane, many levothyroxine pharmacokinetic and pharmacodynamic interactions have been identified, which are summarized in the labeling information for an approved levothyroxine sodium for injection. Clinical history of using Levothyroxine, the route of administration, and the dosing frequency for i.v. levothyroxine for the proposed indication of myxedema coma is available,

Pharmacokinetic nonclinical drug-drug interactions studies in rats d are very limited **(44, 45, 46).** In these studies, interactions occurred between levothyroxine and sodium salicylate (increased metabolism and excretion of levothyroxine), colestipol hydrochloride (decreased absorption of levothyroxine) and cyclosporine A (reduced absorption of cyclosporine A due to levothyroxine induction of P-glycoprotein). In humans, many levothyroxine pharmacokinetic and pharmacodynamic interactions have been identified, which are summarized in the labeling information for an approved levothyroxine sodium for injection. Clinical history of using Levothyroxine, the route of administration, and the dosing frequency for i.v. levothyroxine for the proposed indication of myxedema coma is available.

6.4 General Toxicity

Applicant provided the nonclinical literature on the toxicity of levothyroxine (**TABLE 2.6.6-1**) included toxicity after single and repeat doses of levothyroxine, and studies in pregnant animals and their offspring. These articles describe the effects on the animals treated with L-thyroxine alone, or with L-thyroxine plus placebo, that are most pertinent to toxicity associated with L-thyroxine treatment. None of the referenced studies used the intended clinical i.v. route of administration.

Table 2.6.6- 1 Toxicology Program for Levothyroxine

Reference (Study Number)	Study Type and Duration	Route of Administration	Species	GLP (yes/no)
Hansen, et al. (1992) (2)	Case Report, single dose	Oral	Dog	Unknown (published literature)
Suwanwalaikorn et al. (1996) (3)	Repeat dose study, 20 weeks	i.p.	Sprague Dawley rats	Unknown (published literature)
Yu, et al. (1997) (4)	Repeat dose study, 10 days	i.p.	Sprague Dawley rats	Unknown (published literature)
Mogulkoc and Baltaci, (2006) (5)	Repeat dose study, 4 weeks	i.p.	Sprague Dawley rats	Unknown (published literature)
Ongphiphadhanakul, et al. (1992) (6)	Repeat dose study, 3 weeks	s.c.	Sprague Dawley rats	Unknown (published literature)
Dai, et al. (2002) (7)	Repeat dose study, 10 days	s.c. or i.p.*	Sprague Dawley rats, guinea pigs	Unknown (published literature)
Bhatt, et al. (2007) (8)	Repeat dose study, 3 weeks	s.c.	Wistar rats	Unknown (published literature)
Subudhi, et al. (2008) (9)	Repeat dose study, 30 days	Oral, drinking water	Wistar rats	Unknown (published literature)
Le Traon, et al. (2009) (10)	Repeat dose, dose adjustment every 4 weeks, maintenance dose 22 weeks	Oral	Dog	Unknown (published literature)
Panciera, et al. (1992) (11)	Repeat dose study, 8 weeks	Oral	Dog	Unknown (published literature)
Gallagher and Panciera (2009) (12)	Repeat dose study, 42 days	s.c.	Cat	Unknown (published literature)
Frank et al 2008 (13)	Repeat dose study, 8 weeks	Oral	Horse	Unknown (published literature)
Frénais et al (2009) (14)	Clinical treatment study of diagnosed hyperthyroidism, 53 weeks	No T_4 treatment	Cat	Unknown (published literature)
Liu, et al. (2009) (15)	Repeat dose study, 6 weeks	s.c.	Rat	Unknown (published literature)
Gao, et al. (2009) (16)	Repeat dose study, 7 days	i.p.	Rat	Unknown (published literature)

Table provided by the Applicant

The Applicant stated that no toxicokinetic data of levothyroxine Sodium Injection were found in literature.

The nonclinical toxicities and physiological effects observed in levothyroxine-treated animals are due to exaggerated pharmacological effects of hyperthyroidism. The physiologic responses severe hyperthyroidism in rats include decreased body weight (BW), increased temperature, cardiac hypertrophy (prolonged action potential duration and effective refractory period; increased heart mass, heart rate, systolic pressure, risk of death; ion channel changes), decreased bone mineral density, increased alanine aminotransferase, aspartate aminotransferase and hematocrit, disturbances in carbohydrate metabolism (hyperglycemia, hyperinsulinemia, impaired glucose tolerance,

insulin resistance), and changes in ejaculation. Other indication of thyrotoxicosis include thyroid nodules or enlargement, weight loss, polyphagia, reduced appetite or anorexia, polyuria and/or polydipsia, altered behavior and or demeanor, vomiting, diarrhea, alopecia and changes in hematologic and biochemical parameters (increased alkaline phosphatase [AP], increased alanine aminotransferase [ALT], increased blood urea nitrogen [BUN], leukocytosis, eosinophilia, thrombocytosis, thrombocytopenia, lymphopenia, lymphocytosis). Clinical signs of T4 treatment-induced thyrotoxicosis in dogs include increased temperature, abnormal pupillary light reflexes, vomiting, increased ALT, polyuria, polydipsia, scaling, and altered coat color. Death, presumably from congestive heart failure, has been Such effects include changes in fetal lung maturation, growth stunting, neonatal mortality and suppression of the fetal thyroid. Treatment of neonatal rats with high doses of levothyroxine leads to "neo-T4" syndrome, which includes decreased BW, growth hormone and thyroid stimulating hormone (TSH), increased mortality and derangements in carbohydrate metabolism.

The nonclinical toxicology studies do not identify new findings which impact on the safety of Levothyroxine Sodium Injection in the indicated population.

The Applicant provided nonclinical data based on their literature searches using Medline, and Toxnet. The information to support the toxicological profile of Levothyroxine sodium for injection were based on non-GLP studies and are presented below in Tabulated summaries

6.5 Genotoxicity

No references containing in vitro genotoxicity were found in the literature search. FDA did not require mutagenicity studies for earlier approved Levothyroxine Sodium Injection. The Drug Label (section 13.1) notes that no studies were performed for assessing the genotoxicity.

6.6 Carcinogenicity

No references containing carcinogenicity were found in the literature search. FDA did not require carcinogenicity studies for earlier approved Levothyroxine Sodium Injection. The Drug Label (section 13.1) notes that no studies were performed for assessing the carcinogenicity.

6.7 Reproductive and Developmental Toxicity

No reproductive and developmental toxicities were performed with the proposed drug, Levothyroxine Sodium Injection. The reproductive toxicity studies referenced by the Applicant did not have references to GLP compliances and the route of administration of T4 are other than the intended human i.v. route. These studies cannot be used to draw conclusions on the reproductive and developmental toxicities of the proposed drug. The one study performed with i.v. route was in sheep which are subjected to surgical

thyroidectomy performed at midgestation. The results are provided in the Tabulated Summary Table 2-6-7-11.

Neonatal rats injected with very high dose of levothyroxine showed significantly lower TSH and GH. High dose of levothyroxine in neonate rats produced alteration in carbohydrate metabolism. The effect of levothyroxine, cortisol and diet decreased with the progression of weaning. It was observed that administration of T4 in euthyroid ovine fetus accelerated alvelolization but no accelerate surfactant maturation.

6.8 Other Toxicity Studies

Juvenile Animals Toxicity studies

Applicant stated no studies in which the offspring (juvenile animals) were dosed and/or further evaluated were found in the published literature.

Local Tolerance
Applicant stated no local tolerance studies were found in the published literature.

Other Toxicity Studies
Applicant stated no other toxicity studies were found in the published literature.
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Antigenicity
Applicant stated no antigenicity studies were found in the published literature.

Immunotoxicity
Applicant stated no immunotoxicity studies were found in the published literature.

Mechanistic Studies
No mechanistic studies were found in the published literature.

Dependence
Applicant stated no dependence studies were found in the published literature.

Studies on Metabolites
Applicant stated no studies on metabolites were found in the published literature.

Studies on Impurities
Applicant stated no studies on impurities were found in the published literature.

7 Integrated Summary

FK USA submitted a 505(b)(2) application to market Levothyroxine Sodium Injection for the treatment of myxedema coma. The Levothyroxine Injection ready to use formulation specified in this NDA 210632 (100 µg/5mL, 200 µg/5mL and 500 µg/5mL /vial) has same

active ingredient as the lyophilized LD (Levothyroxine Sodium for Injection-NDA 202231). The difference between the formulations is in the inactive ingredients, degradants, impurities and the container closure system. The excipients in the proposed drug product are simple salts (sodium chloride, tromethamine and sodium iodide) and present in concentrations below the IID limits for the intravenous route of administration and lower than other FDA approved intravenous drug products. The drug substance, Levothyroxine Sodium, USP raw material met the specifications for the proposed Residual Solvents limits. The levels of leachable compounds present in the drug product (based on the Levothyroxine dosing) at expiry would be below acceptable levels. Two degradation products, liothyronine (T3) and 3,5-Diiodo-L-Tyrosine (DIT) were identified and are not of toxicological concern. The overall degradation products in Applicant's Levothyroxine Sodium Injection drug product (b) (4) %) is (b) (4) % more than what was approved in NDA 202231, which is mainly due to higher levels of T3 and DIT. However, T3 and DIT are endogenous compounds. The toxicity of the active T3 hormone is well documented. Therefore, T3 is considered qualified from a nonclinical point of view. DIT is regarded as a metabolite of levothyroxine and therefore, it is qualified based on Q3B(R2). From the pharm/Tox perspective, t*here are no safety concerns based on the amounts of excipients, degradation products and the impurities present in the drug products and the amounts of leachables that may migrate from container materials (vial and stopper).*

The Applicant conducted no nonclinical studies to support the safety and efficacy of Levothyroxine Sodium Injection; instead seeks to rely on the information available from the literature using Medline, and Toxnet searches and FDA's prior findings of safety and efficacy of the LD, Levothyroxine Sodium Injection (NDA 202231). While the Applicant based their nonclinical data, in part, on the literature searches using Medline, and Toxnet, the dependability of the data presented in these non-GLP studies is unclear. Further, the routes of administration of the drug in the animals in those studies were different from the intended clinical i.v. route and none of the nonclinical studies referenced was performed with the Applicant's Levothyroxine Sodium Injection formulation. However, in general, the studies indicate that Levothyroxine Sodium Injection is safe for its intended use.

The drug substance, Levothyroxine sodium in the injection is a synthetic T4 that is chemically identical to endogenous thyroid hormone (T4). Thyroid hormone is required to rescue patients with very low levels of thyroid hormone that result in myxedema coma. Therefore, this ready-to-use formulation is proposed for the treatment of myxedema coma in the hospital setting. The clinical and nonclinical effects of excess thyroid hormone are well known. The animal toxicity of levothyroxine is mostly related to expected exaggerated levothyroxine pharmacology (i.e., hyperthyroidism – decreased body weight, increased heart rate, etc.) at high doses. The Applicant's referenced nonclinical studies from the literature indicate that thyroid hormone primarily functions to increase metabolism (i.e., protein synthesis), growth and development (i.e., growth hormone, bone growth, and neuronal maturation), and catecholamine effect (i.e., adrenaline The animal toxicity of Levothyroxine is mostly related to expected exaggerated levothyroxine pharmacology (i.e., hyperthyroidism (i.e., weight loss, increased food consumption, increased heart rate, increased blood pressure) in thyroid-status compromised or uncompromised animals

(i.e., mice, rats, guinea pigs, rabbits, or dogs) via different routes (i.e., intraperitoneal, subcutaneous, oral, or intravenous).

Pharmacokinetic nonclinical drug-drug interactions studies in animals are very limited**.** In these studies, interactions occurred between levothyroxine and sodium salicylate (increased metabolism and excretion of levothyroxine), colestipol hydrochloride (decreased absorption of levothyroxine) and cyclosporine A (reduced absorption of cyclosporine A due to levothyroxine induction of P-glycoprotein). The nonclinical pharmacokinetic studies did not identify new findings which could impact the safety of Levothyroxine Sodium injection and support Levothyroxine sodium injection for the proposed indication of treatment of myxedema coma. Interactions between thyroid hormone and many drugs are documented. In humans, many levothyroxine pharmacokinetic and pharmacodynamic interactions have been identified, which are summarized in the labeling information for an approved levothyroxine sodium for injection.

Animal studies have not been performed to evaluate the mutagenic and carcinogenic potentials of Levothyroxine Sodium Injection. FDA has not required genotoxic and mutagenic studies for previously approved Levothyroxine sodium injection drug. It is noted that Levothyroxine Sodium Injection is indicated for the treatment of myxedema coma and the treatment is likely to take place in a clinical center. The treatments are acute and for a short duration until the patient is switched to oral treatment. Since, the treatment is acute, there is minimal concern for the requirements for these studies.

Limited amounts of nonclinical information are available on the reproductive and developmental toxicity of levothyroxine. The reproductive toxicity studies referenced by the Applicant did not refer to GLP compliances and the route of administration of T4 are other than the intended human i.v. route. These studies cannot be used to draw conclusions on the reproductive and developmental toxicities of the proposed drug. The one study performed with i.v route was in sheep which are subjected to surgical thyroidectomy performed at midgestation It was observed that administration of T4 in euthyroid ovine fetus at 130 days gestation appears to affect mesenchymal portion of the lungs and accelerated alvelolization but did not accelerate surfactant maturation.

In conclusion, from the Pharm/Tox perspective, there are no safety concerns based on the amounts of excipients, degradation products and the impurities present in the drug products and the amounts of leachables that may migrate from container materials (vial and stopper) that would preclude safe use of this drug for emergency use. The clinical and nonclinical effects of Thyroid hormone are well known. The animal toxicity of Levothyroxine is mostly related to expected exaggerated levothyroxine pharmacology (i.e., hyperthyroidism) at high doses. This therapy is designed to be used only until the patient can tolerate oral therapy. Treatment of myxedema coma is likely to take place in a clinical center. The adverse effects related to Levothyroxine treatment (due to hyperthyroidism) can be monitored and reversed.

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I concur.