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APPLICATION NUMBER:

214047Orig1s000

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:	214047
Supporting document/s:	1 (eCTD Sequence Number: 0001)
Applicant's letter date:	01/31/2020
CDER stamp date:	01/31/2020
Product:	Levothyroxine Sodium Oral Solution
Indication:	Treatment of Thyroid Gland Disorders (hypothyroidism and pituitary TSH suppression)
Applicant:	EMP LEVO US BV
Review Division:	CDER/OCHEN/DDLO
Reviewer:	Parvaneh Espandiari, Ph.D
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1 Executive Summary

1.1 Introduction

EMP Levo US B.V. is seeking marketing approval of Levothyroxine Sodium Oral Solution, 100 mcg/5 mL for the treatment of hypothyroidism and/or pituitary thyrotropin suppression as a 505(b)(2) new drug application. Levothyroxine Sodium Oral Solution is a synthetic compound for which the active product ingredient (levothyroxine) is chemically analogous to endogenous T_4 thyroid hormone.

No animal studies were conducted in support of the NDA 214047 marketing application for levothyroxine oral solution. The Applicant seeks to rely upon the FDA's previous finding of safety and effectiveness of the U.S.- approved, Orange Book-listed drug (LD) Synthroid tablets (NDA 021402, levothyroxine sodium tablets, Abbott Laboratories). To establish a scientific "bridge" between the Applicant's levothyroxine oral solution and the LD, bioavailability clinical studies were conducted to compare the pharmacokinetics between the Applicant's levothyroxine sodium solution and the LD in healthy adults at 600 mcg dose (study #: EMP-P2-777).

Levothyroxine has been marketed extensively for many years and its safety profiles has been well established. Overall, the undesired effects of levothyroxine are related to hyperthyroidism, which are clinically monitorable and reversible in an adequately managed clinical setting.

All identified impurities as well as extractable/leachables were within established acceptable limits.

1.2 Brief Discussion of Nonclinical Findings

The toxicological profile of levothyroxine products is well established. The dose-limiting toxicities with levothyroxine in healthy animals and in animals with compromised thyroid-status via different routes (e.g., intravenous, intraperitoneal, subcutaneous, oral) are exaggerated pharmacological effects due to the excess thyroid hormone activity in euthyroid animals. Hyperthyroidism-related effects include decreased body weight, increased body temperature, cardiac hypertrophy (increased heart mass, heart rate, and ion channel changes), decreased bone mineral density and increased LFTs. These effects are reversible and can be clinically monitored.

1.3 Recommendations

1.3.1 Approvability

Pharmacology/Toxicology recommends approval of Levothyroxine Sodium Oral Solution, 100 mcg/5 mL for the treatment of hypothyroidism and pituitary TSH suppression.

1.3.2 Additional Non-Clinical Recommendations

None

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1.3.3 Labeling

Product labeling should be identical to the PLLR compliant labeling for the LD, Synthroid tablets (NDA 021402) with the exception of the product trade names.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional):
25416-65-3 – hydrate
55-03-8 – anhydrous

Generic Name:
Levothyroxine Sodium

International Non-proprietary Name (INN):
Levothyroxine Sodium

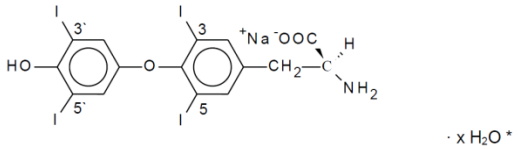
Code Name:
L-T_4 Na

Compendial Name:
Levothyroxine Sodium

Chemical Name:
1. L-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-monosodium salt, hydrate(USP)
2. Monosodium L-thyroxine hydrate (USP)
3. Sodium (2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl] propionate (Ph. Eur.)
4. L-3,3',5,5'-Tetraiodothyronine

Molecular Formula/Molecular Weight:
$C_{15}H_{10}I_4NNaO_4$ with x ~ 5*/798.85 g/mol (anhydrous)
*Levothyroxine Sodium contains a variable amount of water. The pentahydrate is the most stable form.

Structure or Biochemical Description



Pharmacologic Class:
L-thyroxine (T4)

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2.2 Relevant INDs, NDAs, BLAs and DMFs

NDAs: NDA 206977 (Tyrosint-Sol, oral solution); NDA 021116 (Levothroid, Tablet, 2002); NDA 021292 (Levothyroxine Sodium Tablets, 2002); NDA 021301 (Levoxyl, Tablet, 2001); NDA 021342 (LEVO-T, Tablet, 2002); NDA 021924 (Tirosint, Capsule, 2006); NDA 206977 (Tirosint-Sol, 2016); NDA 021210 (Unithroid, Tablet, 2000); NDA 021402 (Synthroid, Tablet, 2002)
DMFs: (b) (4)

2.3 Drug Formulation

Levothyroxine Sodium Oral Solution is an aqueous (clear, colorless to nearly colorless liquid) solution of 100 mcg Levothyroxine Sodium per 5 mL, filled in 100 mL amber glass bottles with a child-resistant, tamper-evident cap, (b) (4) (b) (4). It contains the following excipients: glycerin, citric acid monohydrate, methylparaben sodium, sodium hydroxide and purified water as shown in the table below:

Table 1: Drug Product Composition

Table 1 – Detailed composition of the drug product

Ingredient	Quantity (mg/mL)	Quantity (mg/5 mL)	% (w/v)	Function	Reference
Active Substance					
Levothyroxine sodium[1]	0.020	0.100	0.002	Active ingredient	USP/NF[2]
Excipients					
Glycerin[3]	(b) (4)				USP/NF[2]
Citric acid monohydrate					USP/NF[2]
Methylparaben sodium[4, 5]					USP/NF[2]
Sodium hydroxide					USP/NF[2]
Purified water					USP/NF[2]
Total volume	1 mL	5 mL			

q.s. = quantity sufficient
[1]Adjustment:
The amount of the active ingredient refers to a 100% amount of the substance.
(b) (4)
[2]Current version/edition.
[3] Drug product manufacturer uses in the site documentation the equivalent nomenclature "Glycerin" and "Glycerol" interchangeably.

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2.4 Comments on Novel Excipients

There are no novel excipients in the Applicant's Levothyroxine Sodium Oral Solution, 100 mcg/5 mL product. All excipients are considered safe based on their inclusion in the Agency's Inactive Ingredient Database (IID) or in approved products at similar or greater levels.

Table 2: Levothyroxine Sodium Oral Solution, 100 mcg/5 mL - Inactive Ingredients

Ingredient	Grade	Function*	Quantity (mg/mL)	FDA's IIG Limit; Route of Administration/Dosage Form (as of FDA's IIG update on October 23, 2019)
Glycerin	USP/NF	(b) (4)		1004.8 mg Oral/Solution,
Citric acid monohydrate	USP/NF			460 mg Oral/Tablet, Effervescent
Methylparaben Sodium	USP/NF			3.43 mg/1mL Oral/Suspension
Sodium hydroxide	USP/NF			400 mg Oral/Suspension
Purified water	USP/NF			Not Applicable

* Further detailed information on the role and properties of each of these excipients is addressed in subsection 1.4.2.1 of 3.2.P.2.

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Levothyroxine Sodium Oral Solution contains glycerol (b) (4). At the expected maximum recommended clinical dose (approximately 120 mcg in an 8 Kg child, 300 mcg in adults) the amount of glycerol administered is (b) (4) per day, respectively. As per the latest FDA IID update (July 28, 2020), glycerol maximum daily exposure is 31536 mg. Glycerol is generally recognized as safe (GRAS) and was well tolerated in animal studies, with the only effect being limited to local irritating effects in the gastrointestinal tract in short term rat and dog studies (lowest dose 2,800 and 5,600 mg/kg/day, respectively), likely due its hygroscopic and osmotic effects.

Glycerol was not genotoxic and was not carcinogenic in 2-year dietary studies in rats (up to 10,000 mg/kg/day) and mice. In development and reproduction studies, no effects on fertility and reproductive performance were observed in a two-generation study with glycerol administered by gavage at doses up to 2000 mg/kg/day. No maternal toxicity or teratogenic effects were seen in the rat, mouse or rabbit up to the highest dose tested (1180 mg/kg/day)[1,2].

In addition, similar or higher amounts of glycerol are present in FDA approved drug products for infants (Orfadin and Ravicti), children and adult (Hydrocodone Bitartrate and Acetaminophen Oral Solution (ANDA 200343, the right of reference letter was provided). Based on few published studies in infants, vomiting was the only reported

[1] Re-evaluation of glycerol (E 422) as a food additive. EFSA 2017
[2] OECD SIDS Initial Assessment Report. 2014

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adverse event related to the administration of glycerol via a nasogastric tube[3,4]. Oral doses of glycerol of 10 grams or more have been reported to cause headache, upset stomach and diarrhea (Orfadin label).

2.5 Comments on Impurities/Degradants of Concern

Impurities, degradants, and residual solvents identified were within established acceptable limits.

Table 3: Drug substance impurities specifications

Attribute	Acceptance criteria	Justification
Identification: Identification A *Infrared spectrophotometry* Identification B *HPLC* Identification C (b) (4)	Conforms Retention times of the major peak of Sample solution corresponds to that of the major peak of standard solution Positive	In accordance with drug substance USP monograph and the drug substance manufacturer's specification
Optical rotation[8]	(b) (4)	In accordance with drug substance USP monograph and the drug substance manufacturer's specification
Water content[10]	NMT (b) (4)	In accordance with drug substance USP monograph and the drug substance manufacturer's specification
Assay[8, 10]	(b) (4)	In accordance with drug substance USP monograph and the drug substance manufacturer's specification
Related substances as per the USP monograph Procedure 2 for organic impurities [1, 10]: (b) (4) Individual unspecified impurity Total impurities	NMT (b) (4) NMT NMT NMT NMT NMT NMT NMT NMT NMT	In accordance with drug substance USP monograph ("*Organic Impurities, Procedure 2*") and the drug substance manufacturer's specification. See section 3.2.S.4.5 Table 2 and Table 4. Any potential impurity listed in section 3.2.S.3.2 1 Table 1 (but not stated in the USP monograph under "*Organic Impurities, Procedure 2*") will be monitored under Individual unspecified impurity with a limit of NMT (b) (4)

Attribute	Acceptance criteria	Justification
Residual solvents[9]: (b) (4)	NMT (b) (4) NMT	Tighter than USP <467>/ICH Q3C limit and in accordance with the drug substance manufacturer's specification Acceptance limit is not defined in USP <467>/ICH Q3C. The drug substance is administered in small doses of maximum 300 µg/day, and the acceptance criterion was set in accordance with the drug substance manufacturer's specification as addressed in section 3.2.S.3.2.2.
Microbiological purity[10]: TAMC TYMC	NMT (b) (4) cfu/g NMT cfu/g	In accordance with USP <1111>.

(b) (4)

Applicant's table

[3] Kilpi T. et al. Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. Pediatr Infect Dis J 14(1995): 270-278.
[4] Peltola H. et al. Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial." Clin Infect Dis 2007; 45(10): 1277-1286.

Table 4: Drug Product Specifications

Attribute	Acceptance criteria		Reference to quality standard
	Release	Shelf-life	
1. Appearance	Clear, colorless to nearly colorless liquid free from visible foreign particles		Visual
2. pH	(b) (4)		USP <791>
3. Specific gravity			USP <841> (Method 1)
4. Uniformity of dosage units	AV max. 15.0		USP <905>
5. Deliverable volume	min. 100.0 mL		USP <698>
6. Identification Levothyroxine sodium: HPLC (UV) HPLC (Diode array)	RT of main peak in test solution corresponding to Levothyroxine Sodium complies with RT of main peak in standard solution Levothyroxine Sodium UV spectrum of test solution must comply with the correspondent UV spectrum of standard solution		In-house HPLC method based on USP <621> monograph
7. Identification Methylparaben sodium	RT of main peak in test solution corresponding to Methylparaben sodium complies with RT of main peak in standard solution		In-house HPLC method based on USP <621> monograph
8. Assay of Levothyroxine sodium (% label claim)	(b) (4)		In-house HPLC method based on USP <621> monograph

Attribute	Acceptance criteria		Reference to quality standard
	Release	Shelf-life	
9. Assay of Methylparaben Sodium (% label claim)	(b) (4)		In-house HPLC method based on USP <621> monograph
10. Dose Delivery Volume[1]	The volume delivered should be within ± (b) (4) of the target volume (5 mL) and %RSD should be within (b) (4)		In-house method
11. Degradation products[2]: (b) (4) Any unspecified impurity[3] Total impurities except (b) (4)	NMT (b) (4) NMT NMT	NMT (b) (4) NMT NMT	In-house HPLC method based on USP <621> monograph
12. Microbiological contamination: Total Aerobic Microbial Count Total Combined Yeasts / Molds *Escherichia coli*	Max (b) (4) cfu/mL Max cfu / mL Absent/1 mL		USP <61> USP <1111> USP <62>
13. Package Integrity[4]		Meets test	In-house method
14. Antimicrobial effectiveness testing[5]	Meets test		USP <51>
15. Residual solvents[6]	Complies		USP <467>
16. Elemental impurities[7]	Complies		USP <232> and ICH Q3D

[1]To be performed only on commercial batches.
[2]Term "Related Substances" that is used in some 3.2.P sections or documents (e.g. CoAs) is equivalent to the "Degradation products" term.
[3]Term "Any individual impurity" that is used in some 3.2.P sections or documents is equivalent to the USP nomenclature "any unspecified impurity".
[4]To be performed only on stability.
[5]The efficacy test is intended to be performed only on the registration batches to set the stability baseline and throughout the shelf-life. AET test is not foreseen to be performed during routine batch release or within the scope of any post-approval studies.
[6]Meets USP <467> Option 2 requirements, no routine testing required.
[7]Meets USP <232> ICH Q3D Option 3 requirements, no routine testing required.

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Extractables and Leachables

An extractable study was conducted with cap liner and 5 mL syringe using 25% v/v ethanol/ water, w/v 0.15% citric acid, monohydrate, adjusted to pH 5.5 as a simulant fluid. Based on the extractables profiling, a leachables evaluation was performed on several aged (T=14 months) lots of batch 80570. A toxicological assessment was performed for five species (b) (4) (b) (4) that exceeded the analytical evaluation threshold (AET).

(b) (4)

(b) (4) **toxicity profile**

The oral LD50 in the rat was > 11,656 mg/kg[6]

(b) (4) has been reported to exhibit effects on a wide range of receptors and neurotransmitter systems, suggesting a wide range of CNS effects. The effects of (b) (4) on behaviors, learning, memory, pain perception, body temperature, and depression have been assessed in mice and rats administered a single dose intraperitoneally. In mice administered (b) (4) 5 and 10 mg/kg, dose-dependent reduction in locomotor activity, rearing, and grooming was observed up to 1h post-dose (later time points not examined) at both doses. Increase in the percentage of facilitation in spatial working memory at 5 mg/kg but not at 10 mg/kg in a Ymaze test, and decreased immobility and increased swimming at 10 mg/kg were noted[7]. In rats (30 and 50 mg/kg, IP), (b) (4) facilitated memory extinction in a passive avoidance paradigm,

(b) (4)

and reduced locomotion, core temperature, and pain perception[8]. A NOEL was not identified in either study.

(b) (4) showed no potential for genotoxicity, mutagenicity or clastogenicity[9].

No adverse effects on fertility (7,500 mg/kg/day, diet study)[8] and on sexual behavior (at up to 4 mg/kg/day, intraperitoneal injection)[10] were observed in rats.

In addition, in a QSAR analysis conducted by the Applicant using DEREK Nexus prediction systems, all five identified (b) (4) were predicted to be negative for bacterial mutagenicity.

(b) (4) **PDE Calculation**

PDE was calculated based on (b) (4) LOEL (5 mg/kg, IP) in mice[6]

(b) (4) PDE (µg/day) = 5 (mg/kg) x 50 (kg) / 12 (F1) x 10 (F2) x 10 (F3) X 1 (F4) x 10 (F5)= 0.021 mg/day

- F1=12, for mice to human
- F2=10, for variability between individuals
- F3=10, for studies shorter than 3 months
- F4=1, for no severe toxicity concerns
- F5=10, for using a LOAEL

Table 5: Summary of Leachable Compounds

Leachable Compound	Concentration (ug/product unit)	Maximum daily exposure	Safety Margins based on PDE*
(b) (4)			

(b) (4)

Based on the maximum recommended human dose of Levothyroxine Sodium Oral Solution (300 ug/day), the amount of each individua (b) (4) is within the limits recommended by the Product Quality Research Institute (PQRI)[11]. The cumulative exposure to (b) (4) is 30-fold below the PDE of 21 ug/day, calculated based on the mouse LOAEL of 5 mg/kg. In conclusion, the identified leachable compounds are not expected to pose a risk in the human health under the expected patient exposure to the product.

2.6 Proposed Clinical Population and Dosing Regimen

- Clinical population: pediatric, adolescents, and adults, with thyroid gland disorders
- Dosing Regimen:

1) Adult and adolescents: Starting dose depends on different factors such as age, body weight, cardiovascular status, and concomitant medications (effect may not be reached in 4-6 weeks). In general, the dosing regimen is in the average of 1.6 mcg/kg/day (adjust the dose by increases of 12.5 to 25 mcg every 4 to 6 weeks until the patient is clinically euthyroid and the serum TSH returns to normal). Doses greater than 200 mcg/day are rarely required. Also, an insufficient response to daily doses of greater than 300 mcg/day is rare and may indicate poor compliance, malabsorption, drug interactions, or a combination of these factors. For the elderly patients or patients with underlying cardiac disease, a dose of 12.5 to 25 mcg/day (full replacement dose may be less than 1 mcg/kg/day) is recommended. Also, for patients with severe longstanding hypothyroidism, a dose of 12.5 to 25 mcg/day is suggested (adjust the dose in 12.5 to 25 mcg increases every 2 to 4 weeks until the patient is clinically euthyroid and the serum TSH level is normalized).

2) Pediatric: See table below for daily dose in pediatric patients:

Table 6: Dosing Guidelines for Pediatric Hypothyroidism

AGE	Daily Dose Per Kg Body Weight[a]
0-3 months	10-15 mcg/kg/day
3-6 months	8-10 mcg/kg/day
6-12 months	6-8 mcg/kg/day
1-5 years	5-6 mcg/kg/day
6-12 years	4-5 mcg/kg/day
Greater than 12 years but growth and puberty incomplete	2-3 mcg/kg/day
Growth and puberty complete	1.6 mcg/kg/day
a. The dose should be adjusted based on clinical response and laboratory parameters *[see Dosage and Administration (2.4)* and *Use in Specific Populations (8.4)]*.	

[11] Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. Product Quality Research Institute. August 2006).

Applicant's table

2.7 Regulatory Background

- On October 23, 2015, a PIND meeting was requested, and written responses were granted on December 18, 2015. See below for non-clinical related questions (DARRTS, Pre-IND 127792, 12/18/2015).

2.2. Non-Clinical

EMP Question 4 (Non-Clinical Question 1):
FDA analyzes the excipients by scrutinizing the maximum daily dosage. None of the selected excipients are novel excipients. All selected excipients are under the specified IIG limit for oral solution or syrup route of administration. Additionally, the drug would be dosed and administered at the same levels as the tablet currently is dosed resulting in no change in the amount of active pharmaceutical ingredient being consumed by the patient. For this reason, EMP believes that toxicology studies are not required. Does The Agency agree with this?

FDA Response to Question 4 (Non-Clinical Question 1):
Toxicology studies are not generally required for excipients present at similar or greater amounts in a US approved drug at the maximum recommended dose administered by a similar route and contingent on the duration of dosing. Whether or not the totality of the current safety database will support the proposed clinical bioequivalence study is a review issue pending submission of your IND. See responses to Nonclinical Question 2 for comments regarding your plans to submit a marketing application.

EMP Question 5 (Non-Clinical Question 2):
EMP has extensive experience with this product in Europe. We propose that the safety data (e.g. adverse event reporting) for the product marketed in Europe, which is the same formulation, and indication for use as the proposed product and the product has marketed in the United States as a tablet and injectable dosage form since 2002 be sufficient to demonstrate the safety of the product. Does The Agency agree with this?

FDA Response to Question 5 (Nonclinical Question 2):
We disagree. If you plan to rely upon the Agency's previous finding of safety and efficacy for an approved U.S. drug, e.g., Synthroid, NDA 021402 (see the FDA Orange Book), via the 505(b)(2) regulatory pathway, you will need to provide adequate scientific justification for reliance on the Agency's prior decision of safety for the U.S. listed product(s) you plan to reference. You must submit data necessary to qualify any differences in impurities and degradants with your product compared to the listed drug. Refer to 2.0 General Comments.
Note that U.S. approved drug products published by the Agency in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book") and literature are acceptable sources for a 505(b)(2) application. Non-U.S. approved products (e.g., Evotrox) are not appropriate sources of information for a 505(b)(2) application, because those data are not based on FDA findings of safety and effectiveness. Refer to Section 6.0 for additional information regarding the 505(b)(2) regulatory pathway.

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- Other requested meetings were related to the CMC questions (On May 18, 2016; October 13, 2016; January 24, 2019; November 16, 2018) and clinical questions (August 3, 2017; September 26, 2018; January 24, 2019; November 16, 2018). The Agency granted written responses for these requested.

- During the development, the name of the Applicant was changed from EMP Pharma GmbH (communicated to the Agency on May 15, 2019, PIND 127792) to EMP Levo US B.V.. (b) (4) (b) (4)

3 Studies Submitted

3.1 Studies Reviewed

No nonclinical studies were submitted.

3.3 Previous Reviews Referenced

None

4 Pharmacology

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxin (T_4). In the body, T_4 is secreted by the follicular cells of the thyroid. Synthetic T_4 is identical to the endogenous hormone produced by the human thyroid gland. T_4 is converted to T3 in the liver and kidney. In general, the primary functions of thyroid hormones (T_3 and T_4), upon binding to nuclear thyroid binding receptors, are to increase cardiac function and the basal metabolic rate of the whole organism, with stimulatory effects on the heart, skeletal muscle, liver, and kidney. Thyroid hormones regulate growth and development, particularly of the nervous system, and affect a broad range of other vital metabolic processes.

4.1 Primary Pharmacology

No primary pharmacology studies were required.

4.2 Secondary Pharmacology

No secondary pharmacology studies were required.

4.3 Safety Pharmacology

No safety pharmacology studies were required.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No PK/TK or ADME studies were required.

6 General Toxicology

No repeat-dose toxicity studies were conducted by the Applicant with levothyroxine oral solution.

In general, most toxicities observed in animals with other levothyroxine formulations are exaggerated pharmacological effects due to the excess thyroid hormone activity in euthyroid animals. These effects include decreased body weight, increased body temperature, cardiac hypertrophy (increased heart mass, heart rate, and ion channel changes), decreased bone mineral density and increased LFTs.

7 Genetic Toxicology

No genetic toxicology studies were conducted by the Applicant.

8 Carcinogenicity

No carcinogenicity studies were conducted by the Applicant.

Synthetic T_4, the levo isomer of thyroxine, is chemically identical to thyroxine produced by the human thyroid gland.

9 Reproductive and Developmental Toxicology

No reproductive studies were conducted by the Applicant.

It is generally known that maternal thyroid agent hormones do not readily cross the placenta into the fetal circulation, and clinical experience does not indicate any adverse effect on the fetus when thyroid agents are administered during pregnancy.

11 Integrated Summary and Safety Evaluation

The Applicant seeks approval for Levothyroxine Sodium Oral Solution, 100 mcg/5 mL (NDA # 214047) for the treatment of hypothyroidism and/or pituitary thyrotropin stimulating hormone (TSH) suppression under the 505(b)(2) NDA approval pathway with Synthroid tablets (NDA 021402, levothyroxine sodium tablets) as the listed drug (LD). No animal studies were conducted to support the marketing application for the proposed levothyroxine formulation. Therefore, the Applicant relies on the Agency's previous findings of safety and effectiveness for previously approved LD (Synthroid®) and clinical bioavailability studies for comparing the pharmacokinetics of these two levothyroxine formulations.

The Applicant's levothyroxine formulation consists of the active ingredient of levothyroxine sodium (synthetic T_4). The safety profiles of levothyroxine have been established in animals as well as in humans where there is long-standing precedent for replacement hormone therapy for reduced or absent thyroid gland function.

In general, the most common findings with administration of levothyroxine to healthy animals and those with compromised thyroid function are those associated with an

exaggerated pharmacologic response to excess thyroid hormone (i.e., thyrotoxicosis), characterized by weight loss, increased food consumption, elevated heart rate, higher blood pressure, etc.

The mutagenic or carcinogenic potential of levothyroxine sodium has not been evaluated with animal studies, since the synthetic hormone is identical to the endogenous hormone. No animal studies have been conducted to determine the effect of levothyroxine on fertility or reproduction. Hypothyroidism is detrimental to human reproduction.

There are no safety concerns regarding the inactive ingredients. The drug product's impurity profile appears acceptable, based on compendial (USP) drug substance/product specifications and evaluation procedures. The levels of identified leachable compounds were evaluated and determined to be within acceptable limits.

There are no nonclinical safety concerns regarding the use of levothyroxine oral solution based on available data that should preclude approval of this application.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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10/16/2020 11:40:38 AM

FEDERICA BASSO
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I concur