CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215809Orig1s000

CLINICAL REVIEW(S)

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Levothyroxine sodium oral solution is a synthetic thyroxine hormone product indicated as replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism, and as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

On June 30, 2021, Mylan Pharmaceuticals (Applicant) submitted a New Drug Application (NDA) for levothyroxine sodium oral solution 150 mcg/5mL under section 505(b)(2) of the of the Federal Food, Drug, and Cosmetic (FD&C) Act for the treatment of hypothyroidism and TSH suppression, relying upon the listed drug (LD) Synthroid (NDA 021402, approved 2002).

The Applicant's submission includes:

1. A bioequivalence study (LVOS-1-19094) to establish the bioequivalence of Levothyroxine Sodium oral solution against Synthroid after a single oral dose administration under fasting conditions.
2. A physicochemical assessment evaluating the Levothyroxine sodium oral solution drug substance and drug product.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted one bioequivalence (BE) trial, LVOS-1-19094, conducted to establish bioequivalence between Levothyroxine sodium oral solution 150 mcg/5 mL and Synthroid 300 mcg tablet following a dose of 600 mcg under fasting conditions. The pharmacokinetic data from this trial was reviewed by the clinical pharmacology reviewer, Sze W Lau, RPh, PhD, who recommends approval. I agree with Dr. Lau's assessment.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Levothyroxine sodium oral solution is a synthetic thyroxine hormone product indicated as replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism, and as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

Hypothyroidism is a condition of low thyroid hormone levels and presents with a constitution of symptoms such as fatigue, cold sensitivity, constipation, weight gain, bradycardia, dry skin, muscle cramps, and voice changes. Hypothyroidism is a serious condition, as if left untreated, it can advance to myxedema coma, a state of severely decompensated hypothyroidism that may result in multiple organ injuries and even death.

Levothyroxine (LT4) is considered the standard of care for the treatment of hypothyroidism, and multiple levothyroxine products have been approved for this use. The goal of treatment is to normalize thyroid hormone levels, improve the biological and physiologic markers of hypothyroidism and to avoid overtreatment. The starting dose of levothyroxine should be individualized based on a patient's body weight, pregnancy status, etiology of hypothyroidism, age, degree of thyroid hormone deficiency and other risk factors such as presence of cardiac disease. The LT4 dose should be adjusted to maintain serum thyroid hormone levels in the normal range.

Levothyroxine is a Narrow Therapeutic Index (NTI) drug. Hence, small variations in the blood thyroid hormone concentrations, which can occur upon substitution to a drug product of a different potency or bioavailability, can either lead to over treatment or inadequate treatment. Over-treatment can cause iatrogenic thyrotoxicosis, which may result in cardiac arrhythmia, weight loss, heat intolerance, diarrhea, tremors, anxiety, and decreased bone density. On the other hand, inadequate treatment can lead to worsening signs/symptoms of hypothyroidism.

The Applicant is seeking approval of a new levothyroxine sodium oral solution via the 505(b)(2) regulatory pathway, and submitted one bioequivalence (BE) trial, LVOS-1-19094, conducted to establish bioequivalence between Levothyroxine sodium oral solution and Synthroid. Trial LVOS-1-19094 established the bioequivalence between Levothyroxine sodium oral solution 150 mcg/5 mL and Synthroid 300 mcg tablet following a dose of 600 mcg under fasting conditions. No new safety findings were observed during this trial, and the safety profile of Levothyroxine sodium oral solution remains favorable from a clinical perspective.

Therefore, I recommend approval of NDA 215809.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hypothyroidism is a condition of low thyroid hormone levels. • Clinical signs and symptoms of hypothyroidism include fatigue, cold sensitivity, constipation, weight gain, bradycardia, dry skin, muscle cramps, and voice changes. • Hypothyroidism, if left untreated, can advance to myxedema coma, a state of severely decompensated hypothyroidism that may result in multiple organ injuries and even death.	Hypothyroidism is a serious chronic condition, characterized by a constitution of symptoms, which if untreated can be life threatening.
Current Treatment Options	• FDA-approved therapies for hypothyroidism include levothyroxine and liothyronine. • Levothyroxine, considered standard of care for treatment of hypothyroidism, is a narrow therapeutic index drug, and small variations in the blood thyroid hormone concentrations, which can occur upon substitution to a drug product of a different potency or bioavailability, can either lead to over treatment or inadequate treatment. • The goal of treatment is to normalize thyroid hormone concentrations, improve the biological and physiologic markers of hypothyroidism and to avoid overtreatment.	Levothyroxine is the standard of care for the treatment of hypothyroidism and is considered a narrow therapeutic index drug.
Benefit	• Benefits of treatment with levothyroxine in patients with hypothyroidism include improvement in symptoms such as fatigue, cold sensitivity, constipation, weight gain, bradycardia, dry skin, and muscle cramps.	Treatment of patients with hypothyroidism with levothyroxine results in an improvement in various symptoms of hypothyroidism.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Overall, levothyroxine therapy is well tolerated • Adverse events (AEs) typically occur due to over-treatment and are consistent with signs and symptoms of hyperthyroidism, such as cardiac arrhythmia, tachycardia, increased blood pressure, nervousness, diarrhea, abdominal cramps, weight loss, increased appetite, hyperthermia/heat intolerance, tremors, anxiety, and decreased bone density.	Levothyroxine therapy is generally well tolerated. AEs typically occur due to over-treatment and are consistent with the signs and symptoms of hyperthyroidism. These AEs are adequately conveyed in product labeling for all levothyroxine products.

1.4. Patient Experience Data

Not applicable. No Patient Experience Data was submitted in this Application.

2. Therapeutic Context

2.1. Analysis of Condition

Hypothyroidism is a condition of low thyroid hormone levels and presents with a constitution of symptoms such as fatigue, cold sensitivity, constipation, weight gain, bradycardia, dry skin, muscle cramps, and voice changes.[1] Hypothyroidism is a serious condition, as if left untreated, it can advance to myxedema coma, a state of severely decompensated hypothyroidism that may result in multiple organ injuries and even death.[2]

In the United States, the prevalence of hypothyroidism in individuals aged 12 and older is estimated to be between 0.3% and 9.5% in various studies.[3,4,5,6] Women are at a greater risk of developing hypothyroidism compared to men. In one study, the incidence of hypothyroidism was 3.5 per 1000 survivors per year in women, and 0.6 per 1000 survivors per year in men.

Hypothyroidism can either be of primary or secondary etiology. Primary hypothyroidism is characterized by low levels of thyroxine (T4) and triiodothyronine (T3) along with elevated levels of TSH. Common causes of primary hypothyroidism include autoimmune thyroiditis (Hashimoto's thyroiditis) and environmental iodine deficiency. Central hypothyroidism occurs due to hypothalamic-pituitary disease, and is characterized by low T4 and low T3, in the setting of low or abnormally normal TSH levels.

Levothyroxine is considered the standard of care for the treatment of hypothyroidism.[7] The goal of treatment is to normalize thyroid hormone concentrations, improve the biological and physiologic markers of hypothyroidism and to avoid overtreatment.

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[1] Garber, JR et. al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American association of clinical endocrinologists and the American thyroid association. *Endocrine Practice.* 2012; 18:989-1028
[2] Rhodes Wall, C. Myxedema Coma: Diagnosis and Treatment. *American Family Physician.* 200; 62(11):2485-2490
[3] Hollowell JG et al. Serum TSH, T(4), and thyroid antibodies in the United states population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *Journal of Clinical Endocrinology and Metabolism.* 2002; 87: 489-499
[4] Canaris GJ et. al. The Colorado thyroid disease prevalence study. *Archives of Internal Medicine.* 2000; 160:526-534
[5] Sawin CT et. al. The aging thyroid. Thyroid deficiency in the Framingham Study. *Archives of Internal Medicine.* 1985;145:1386-1388
[6] Vanderpump MP, et. al. Epidemiology and prevention of clinical and subclinical hypothyroidism. *Thyroid.* 2002;12:839-847
[7] Jonklaas, J et. al. Guidelines for the Treatment of Hypothyroidism. *Thyroid*. 2014; 24:1670-1751

The starting dose of levothyroxine should be individualized, based on a patient's body weight, pregnancy status, etiology of hypothyroidism, age, degree of thyroid hormone deficiency and other risk factors, such as presence of cardiac disease. TSH levels should be measured 4-6 weeks after initiation of therapy or after any change in dosage and are used to guide further dose adjustments.

Over-treatment can cause iatrogenic thyrotoxicosis, which may result in cardiac arrhythmia, weight loss, heat intolerance, diarrhea, tremors, anxiety, and decreased bone density. On the other hand, inadequate treatment can lead to worsening signs/symptoms of hypothyroidism.

Levothyroxine is a narrow therapeutic index (NTI) drug.[8] Hence, small variations in the blood thyroid hormone concentrations, which can occur upon substitution to a drug product of a different potency or bioavailability, can either lead to over treatment or inadequate treatment.

In conclusion, hypothyroidism is a serious chronic condition characterized by a constitution of symptoms that, if left untreated, can be life threatening, and the primary treatment for hypothyroidism, levothyroxine, is an NTI drug.

2.2. Analysis of Current Treatment Options

FDA-approved therapies for the treatment of hypothyroidism include multiple formulations of levothyroxine and liothyronine. Refer to Table 1 for a list of currently available levothyroxine products approved to treat hypothyroidism.

Table 1: FDA-approved therapies for Hypothyroidism

Product (s) Name (Application number/Company)	Dosage forms available	Year of Approval	Approved dosing
Approved levothyroxine therapies			
Unithroid (NDA 021210 – Stevens J)	Tablet	2000	The dose for hypothyroidism or pituitary TSH suppression depends on a variety of factors including: the patient's age, body weight, cardiovascular status, concomitant medical conditions, concomitant medications, co-administered food and the specific nature of the condition being treated. Dosing must be individualized to

[8] Guidance for Industry: Levothyroxine sodium tablets – In Vivo Pharmacokinetic and Bioavailability studies and In Vitro Dissolution Testing. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). December 2000.

Product (s) Name (Application number/Company)	Dosage forms available	Year of Approval	Approved dosing
			account for these factors and dose adjustments made based on periodic assessment of the patient's clinical response and laboratory parameters. Peak therapeutic effect may not be attained for 4 to 6 weeks.
Levoxyl (NDA 021301 – King Pharms)	Tablet	2001	Same as above.
Synthroid (NDA 021402– Abbvie)	Tablet	2002	Same as above.
Euthyrox (NDA 021292 – Provell)	Tablet	2002	Same as above.
Levo-T (NDA 021342– Cediprof, Inc.)	Tablet	2002	Same as above.
Thyro-Tabs (NDA 021116 – Alvogen)	Tablet	2002	Same as above.
Levothyroxine sodium (ANDA 076187 – Mylan)	Tablet	2002	Same as above.
Levolet (NDA 021137 – Genus Lifescience)	Tablet	2003	Same as above.
Tirosint (NDA 021924 – Institut Biochimique)	Capsule	2006	Same as above.
Tirosint – Sol (NDA 206977 – Institut Biochimique)	Solution	2016	Same as above.
Levothyroxine sodium (ANDA 209713 – Lupin)	Tablet	2019	Same as above.

Product (s) Name (Application number/Company)	Dosage forms available	Year of Approval	Approved dosing
Thyquidity (NDA 214047 – Vistapharm)	Solution	2020	Same as above.
Levothyroxine sodium (ANDA 212399 – Accord Healthcare)	Tablet	2020	Same as above.
Levothyroxine sodium (ANDA 211369 – Teva)	Capsule	2020	Same as above.

NDA = New Drug Application
ANDA = Abbreviated New Drug Application
Source: Approved labels at: drugs@FDA and https://dailymed.nlm.nih.gov

In conclusion, there are multiple approved and available levothyroxine products for the treatment of hypothyroidism.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Levothyroxine sodium oral solution 150 mcg/5 mL manufactured by Mylan Pharmaceuticals is not currently marketed in US.

3.2. Summary of Presubmission/Submission Regulatory Activity

On October 10, 2016, Axar Pharmaceuticals, Inc. (the Applicant at that time) submitted a meeting request under PIND (b) (4) seeking guidance on the development plan, the appropriate regulatory pathway, and the proposed drug-device combination for Levothyroxine sodium oral solution approval, to which the Division provided written responses (see final written responses in DARRTS dated 12/8/2016, and Advice/Information request correspondence dated 2/9/2017).

On January 30, 2017, the Applicant submitted a proposed bioavailability study under PIND (b) (4) In response, the Division advised the Sponsor to submit an IND including a full protocol (see advice letter dated 2/9/2017 in DARRTS). On 4/9/2018, PIND (b) (4) was closed by the Agency because no correspondence had been received from Axar in over one year. Axar has since formed a joint venture under the name TAP Pharmaceuticals AG.

On September 27, 2018, TAP Pharmaceuticals AG (the Applicant at that time) submitted a relative bioavailability study protocol to establish a "bridge" between the test product Levothyroxine sodium oral solution and the listed drug (LD) Synthroid under IND 141382. The study was deemed safe to proceed.

On 8/30/2019, the Applicant requested a type C meeting seeking further guidance regarding drug/device combination product design, human factors studies of the proposed drug-device delivery system and Chemistries, Manufacturing, and Controls (CMC) data required for future NDA submission, for which the Division provided written responses (see final written responses in DARRTS, dated 11/4/2019).

On January 20, 2020, TAP Pharmaceuticals AG transferred ownership to Mylan Pharmaceuticals, Inc (Mylan).

(b) (4)

On June 30, 2021, Mylan Pharmaceuticals (Applicant) submitted a New Drug Application (NDA) for Levothyroxine sodium oral solution 150 mcg/5mL under section 505(b)(2) of the of the Federal Food, Drug, and Cosmetic (FD&C) Act for the treatment of hypothyroidism and TSH suppression, relying upon the listed drug (LD) Synthroid (NDA 021402, approved 2002).

3.3. Foreign Regulatory Actions and Marketing History

A new drug marketing application for Mylan's Levothyroxine sodium oral solution has not been submitted outside of the US in the past.

4. Sources of Clinical Data and Review Strategy

4.1. Table of Clinical Studies

Table 2: Clinical Studies submitted in this Supplement

TYPE OF STUDY	STUDY IDENTIFIER	LOCATION OF STUDY REPORT	OBJECTIVE(S) OF THE STUDY	STUDY DESIGN AND TYPE OF CONTROL	TEST PRODUCT(S); DOSAGE REGIMEN; ROUTE OF ADMINISTRATION	NUMBER OF SUBJECTS	HEALTHY SUBJECTS OR DIAGNOSIS OF PATIENTS	DURATION OF TREATMENT	STUDY STATUS; TYPE OF REPORT
BE	LVOS-1-19094	5.3.1.2	A Randomized, Open-Label, Two-Treatment, Two-Period, Crossover Study to Evaluate the Relative Bioavailability of a Test Formulation of Levothyroxine Sodium Oral Solution (DPT Laboratories, Ltd.) Compared to Synthroid® (levothyroxine sodium) Tablets, USP (AbbVie Inc.) Following a Single 600 µg Oral Dose to Healthy Adult Subjects under Fasted Conditions	open-label, single-dose, randomized, two-treatment, two-period, crossover study	A= Levothyroxine Sodium Oral Solution, 150 µg/5mL (DPT Laboratories, Inc., Lot: PDS-1C) Dose: 600 µg (20 mL × 150 µg/5 mL) B= Synthroid® Tablets USP, 300 µg (AbbVie Inc., Lot: 1109288) Dose: 600 µg (2 × 300 µg/tablet)	36 Dosed 32 completed	Healthy Subjects	Single Dose	Complete: Full

Source: Tabular Listing of All Clinical Studies submitted by the Applicant, Module 5.2

4.2. Review Strategy

The Applicant has submitted one BE trial in the current submission, Trial LVOS-1-19094, to establish the bioequivalence of Levothyroxine sodium oral solution against Synthroid after a single oral dose administration under fasting conditions. Refer to Table 2.

This review will primarily focus on the safety data from this trial, and the BE data from this trial will only be briefly summarized. For a detailed discussion of the BE results, refer to the review by the clinical pharmacology reviewer, Sze W Lau, RPh, PhD.

5. Review of Trial LVOS-1-19094 to support bioequivalence between Levothyroxine sodium oral solution and Synthroid

5.1. Trial design

Trial LVOS-1-19094 was an open-label, single-dose, randomized, two-treatment, two-period, crossover trial in 36 healthy male and female subjects.

The primary objective of this trial was to establish the bioequivalence of Levothyroxine sodium oral solution 150 mcg/5 mL and Synthroid (levothyroxine sodium) tablets 300 mcg after a single oral dose administration of 600 mcg dose of levothyroxine under fasting conditions.

During each period, the subjects were admitted to the clinical site at least 16 hours before dose administration in each study period. On study day 1, each subject received either a single, oral dose of 600 mcg (20 mL of 150 μg/5 mL oral solution) of the Test product (Levothyroxine sodium oral solution, 150 μg/5 mL) or the Reference product (Synthroid). Dosing occurred following an overnight fast of at least 10 hours. Following a washout period of 35 days, all subjects returned to the clinical facility to be dosed with the next study treatment as per the randomization. In each study period, blood samples were collected at pre-dose (-0.5, -0.25, and 0-hour) and post-dose at study hours 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0, 18.0, 24.0 and 48.0 hours. The subjects were allowed to leave the clinical facility after the 24-hour blood sample collection and returned to the clinical facility for the scheduled blood sample collection post-dose at study hour 48. Refer to Table 3 for a schedule of assessments.

Table 3. Study design and Schedule of Assessments in Trial LVOS-1-19094

Study Phase	Screening	Study Days (Periods I and II)				
Activity	Within 28 days of Day 1	Day -1	Day 1	Day 2	Day 3	End of Study Day 3 Period II
Informed Consent	X					
Social, Medical History and Demographic Data	X					
Physical Examination	X					X
Virology Testing	X					
FSH testing, if applicable[1]	X					
Clinical Lab Tests[2]	X					X
12 Lead ECG[3]	X		X			X
Inclusion/Exclusion	X					
Eligibility		X				
Subject Status Update					X	
Vital Signs[3]	X	X	X	X	X	
Drug, Alcohol, and Cotinine Screen[4]	X	X				
Serum Pregnancy Test[5]	X	X				X
Prior and Concomitant Medication Query	X	X	X	X	X	X
Confinement[6]		X	X	X		
Dosing[7]			X			
PK sampling[8]			X	X	X	
Adverse Events[9]	X	X	X	X	X	X

[2]Laboratory evaluation includes: Chemistry, Hematology and Urinalysis at Screening and End-of-Study; TSH, T3, T4, and virology at Screening only
Source: Study Protocol, Trial LVOS-1-19094, Appendix 9.2

Key Inclusion Criteria:

- Males and non-pregnant females 18-50 years of age, inclusive, with a minimum body weight of 50 kg (110 lbs.) and a Body Mass Index (BMI) of 18-30 kg/m2, inclusive.
- Female subjects of non-childbearing potential [e.g., surgically sterile (bilateral oophorectomy or hysterectomy at least 6 months before initial dosing); non-surgically sterile (Essure® device placement at least 3 months prior to initial dosing); at least 1 year postmenopausal and had a documented FSH level ≥ 40 mIU/mL at screening]
- Female subjects of childbearing potential who agreed to utilize one of the following forms of non-hormonal contraception during the timeframe indicated: abstinence (i.e., sexually inactive) or double-barrier contraception (male condom with spermicide or cap, diaphragm with spermicide, etc.) from screening to at least 30 days after the last dose of study drug; intrauterine device (IUD) in place for at least 3 months before initial dosing and male

condom or spermicide from screening (signing of informed consent) and for at least 30 days after the last dose of study drug in this study.
- Good health as determined by lack of clinically significant abnormalities in health assessments performed at screening.

Key Exclusion Criteria:

- Females who were pregnant, lactating or likely to become pregnant during the study.
- History of allergy, sensitivity, or idiosyncrasy to levothyroxine or components of the study drug, or history of any drug hypersensitivity or intolerance.
- Significant history or current evidence of chronic infectious disease, system disorders, organ dysfunction, especially cardiovascular (e.g., myocardial infarction, angina, cardiac arrhythmias, coronary artery disease), adrenal insufficiency, pernicious anemia, diabetes, renal or hepatic disorders, or clotting disorders.
- History or current evidence of thyroid cancer or thyroid disease including hyperthyroidism, hypothyroidism, thyroid nodules, goiter, or thyroid treatment.
- Abnormal values for T4, T3 or TSH at screening.
- Subject has had a cholecystectomy (i.e., surgical removal of the gallbladder).
- Clinically significant history or presence of gastrointestinal disease or history of malabsorption within the last year.
- History of psychiatric disorders occurring within the last two years, which required the subject to be hospitalized or treated with medication.
- Presence of a medical condition requiring regular treatment with prescription drugs.
- Use of pharmacologic agents known to significantly induce or inhibit drug metabolizing enzymes within 30 days before initial dosing.
- Receipt of any drug as part of a research study within 30 days before initial dosing.
- Drug or alcohol addiction requiring treatment during the past 12 months.
- History of excessive alcohol consumption (on average more than 14 units of alcohol/week) during the past 12 months.
- Donation or significant loss of whole blood (480 mL or more) within 30 days or plasma within 14 days before initial dosing.
- Difficulty in swallowing an oral solution or solid dosage forms such as tablets or capsules.
- Positive test for HIV, Hepatitis B surface antigen or Hepatitis C antibody.
- Positive test results for drugs of abuse or cotinine at screening.
- If female, had a positive pregnancy test at screening.
- Use of tobacco- or nicotine-containing products within 1 year before initial dosing.

5.2. Review of Bioequivalence

Disposition:

A total of 36 subjects were included in the study, with 32 subjects successfully completing the study and being included in the pharmacokinetic and statistical analysis plan. Four (4) subjects discontinued the study due to protocol deviations, with 3 subjects due to positive urine drug screen results and 1 subject due to indeterminate pregnancy test results.

Results:

Bioequivalence between Levothyroxine sodium oral solution and Synthroid was to be established if the following criteria were met:

- Using two one-sided tests, the ratio of geometric least square (LS) means with corresponding 90% confidence intervals (CI), calculated form the exponential of the difference between the Test and Reference products for the ln-transformed parameters maximum observed serum concentration (C_{max}) and area under the serum concentration time curve from 0 to 48 hours (AUC_{0-48}) were all within the 80 to 125% bioequivalence range for both comparisons of interest

Refer to Table 4 and Table 5 for Cmax, time of maximum observed serum concentration (T max) and AUC 0-48 for Levothyroxine sodium oral solution (Treatment A) and Synthroid (Treatment B), respectively.

Table 4. Mean Baseline Corrected Levothyroxine Pharmacokinetic Parameters

Parameter	Treatment A = Levothyroxine Sodium Oral Solution, 150 µg/5 mL (Mylan; PDS-1C) (Levothyroxine)		Treatment B = Synthroid® Tablet USP, 300 µg (AbbVie; Lot 1109288) (Levothyroxine)		LSMEANS Ratio (A/B)‡		90% Confidence Interval†
	N	Geometric LS Mean Arithmetic Mean (%CV)	N	Geometric LS Mean Arithmetic Mean (%CV)	N		
pAUC48 (ng•hr/mL)	32	1858.62 1885.26 (17.54%)	32	1601.27 1655.53 (24.39%)	32	1.16	110.51% – 121.91%
CPEAK (ng/mL)	32	70.69 72.21 (21.33%)	32	64.88 66.76 (23.25%)	32	1.09	103.12% –115.11%
Tpeak (hr)*	32	2.00 (1.00 – 3.52)	32	2.00 (1.02 – 4.00)	--		--

‡ Ratio (A/B) = $e^{[\text{LSMEAN of (LNA – LNB)}]}$; †Used Natural Log Transformed Parameter;
**Arithmetic Mean (%CV); *median (min-max);

Source: Clinical Study Report, Trial LVSOS-1-19094, Table 14.6, Appendix 16.2.6

Table 5. Mean Baseline Uncorrected Levothyroxine Pharmacokinetic Parameters

Parameter	Treatment A = Levothyroxine Sodium Oral Solution, 150 µg/5 mL (Mylan; PDS-1C) (Levothyroxine)		Treatment B = Synthroid® Tablet USP, 300 µg (AbbVie; Lot 1109288) (Levothyroxine)		LSMEANS Ratio (A/B)‡		90% Confidence Interval†
	N	Geometric LS Mean Arithmetic Mean (%CV)	N	Geometric LS Mean Arithmetic Mean (%CV)	N		
pAUC48 (ng•hr/mL)	32	5541.39 5599.55 (14.49%)	32	5353.28 5413.27 (14.95%)	32	1.04	101.43% – 105.64%
CPEAK (ng/mL)	32	147.84 149.55 (15.50%)	32	143.30 145.04 (15.34%)	32	1.03	100.25% –106.18%
Tpeak (hr)*	32	2.00 (1.00 – 3.52)	32	2.00 (1.02 – 4.00)	--		--

‡ Ratio (A/B) = e [LSMEAN of (LNA – LNB)]; †Used Natural Log Transformed Parameter;
**Arithmetic Mean (%CV); *median (min-max);

Source: Clinical Study Report, Trial LVSOS-1-19094, Table 14.7, Appendix 16.2.6

Per the Applicant's analysis, the Test to Reference ratio (A/B) and corresponding 90% CI for geometric LS means for C_{max} and AUC_{0-48} were within the bioequivalence range of 80-125%, therefore, bioequivalence between Levothyroxine oral solution and Synthroid was established.

For a detailed discussion of the bioequivalence results, refer to the review of the clinical pharmacology reviewer, Sze W Lau, RPh, PhD.

5.3. Review of Safety

5.3.1. Safety Review Approach

The Applicant has submitted one BE trial in the current submission. Trial LVSOS-1-19094 established the bioequivalence of Levothyroxine sodium oral solution against Synthroid, after a single oral dose. This study enrolled healthy, adult subjects.

5.3.2. Review of the Safety Database

Overall Exposure

A total of 36 healthy adult subjects were enrolled in the trial, of whom 33 (92%) subjects received 1 dose of Levothyroxine sodium oral solution and 35 (97%) subjects received 1 dose of Synthroid.

Adequacy of the safety database:

Not applicable. The trial that was submitted by the Applicant was conducted in healthy adult

volunteers to establish the bioequivalence between Levothyroxine sodium oral solution and Synthroid. Hence, this trial only provides supportive evidence for the safety of this product in patients with hypothyroidism.

5.3.3. Adequacy of Applicant's Clinical Safety Assessments

The Applicant's clinical safety assessments were adequate. Subjects were confined to the clinical research facility for at least 10 hours prior to drug administration and until 24 hours post-dose in each study period. Safety assessments included vital signs measurements, clinical laboratory tests (hematology, general biochemistry including liver function tests, TSH, and free T4), electrocardiograms (ECG) and recording of adverse events.

Issues Regarding Data Integrity and Submission Quality

None.

Categorization of Adverse Events

The Applicant's definitions of adverse events (AE) and serious adverse events (SAEs) in the protocol were acceptable. AEs were defined as 'any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not related to the investigational product.' SAEs were defined as an AE that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event that may have jeopardized the subject or may have required intervention to prevent one of the other outcomes listed above.

Routine Clinical Tests

Routine clinical laboratory tests, including hematology and biochemistries, and thyroid function tests, including TSH and free T4, were obtained at pre-specified time points during the trial.

5.3.4. Safety Results

Deaths

During the trial, no deaths were reported.

Serious Adverse Events

During the trial, no serious adverse events were reported.

Dropouts and/or Discontinuations Due to Adverse Effects

During the trial, no treatment emergent adverse events (TEAEs) that lead to treatment discontinuation were reported.

Significant Adverse Events

There were no severe adverse events reported during the trial.

Treatment Emergent Adverse Events and Adverse Reactions

According to the Applicant's analysis, 11 (30%) subjects experienced a total of 17 TEAEs over the course of the study: 12 TEAEs occurred in 9 (27%) subjects after administration of Levothyroxine sodium oral solution compared to 4 TEAEs in 4 (11%) subjects after administration of Synthroid (1 TEAE of blood iron decreased could not be adjudicated because clinical labs were only collected at screening and study exit (i.e., after exposure to both study drugs)). All reported AEs were mild in severity. The rate of TEAEs was low and the majority of TEAEs occurred as single subject events, except for throat irritation [3 out of 33 (9%) subjects in Levothyroxine sodium oral solution arm vs. 0 subjects in Synthroid arm], diarrhea and nausea [each in 2 out of 33 (6%) subjects in Levothyroxine sodium oral solution arm vs. 0 subjects in Synthroid arm]. Refer to Table 6.

Table 6. Summary of Treatment-Emergent Adverse Events by System Organ Class

System Organ Class **MedDRA Preferred Term**	**Treatment A** **(Levothyroxine sodium solution)** **(N = 33)** **n (%)**	**Treatment B** **(Synthroid)** **(N = 35)** **n (%)**
Nervous system disorders		
Headache	0	1 (3)
Lethargy	1 (3)	0
Dizziness	1 (3)	0
Somnolence	1 (3)	0
Gastrointestinal disorders		
Diarrhea	2 (6)	0
Abdominal pain	1 (3)	1 (3)
Nausea	2 (6)	0
Respiratory, thoracic and mediastinal disorders		
Epistaxis	1 (3)	0

Throat irritation	3 (9)	0
General disorders and administration site conditions		
Feeling jittery	0	1 (3)
Investigations		
Blood iron decreased	0	1 (3) [#]
Heart rate increased	0	1 (3)

N= total number of subjects exposed to treatment; n = number of subjects with TEAE; %: percent of subjects with TEAE; MedDRA Preferred Term Version 22.0
*****Adverse reaction "Abdominal pain" included PTs of "Abdominal discomfort" and "Abdominal pain upper"
[#] One subject experienced AE of blood iron decreased; etiology could not be established, because clinical labs were only collected at screening and study exit (i.e., after exposure to both study drugs).
Source: Adapted after Table 12.4, Clinical Study Report, Trial LVSOS-1-19094

Overall, the safety profile of Levothyroxine sodium oral solution observed in the trial is consistent with expected adverse events that may be seen after over-treatment with levothyroxine. No new safety findings were observed during the trial. The AEs that were observed are consistent with AEs that are currently listed in Section 6 (Adverse Reactions) of the Synthroid label.

Laboratory Findings

No new safety concerns with respect to laboratory findings were observed during the trial.

Vital Signs

No new safety concerns with respect to vital signs were observed during the trial.

Electrocardiograms (ECGs)

No new safety concerns with respect to ECGs were observed during the trial. ECG-related TEAEs were not observed during the trial.

Immunogenicity

Not applicable.

5.3.5. Analysis of Submission-Specific Safety Issues

Not applicable.

5.3.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

5.3.7. **Safety Analyses by Demographic Subgroups**

Not applicable.

5.3.8. **Specific Safety Studies/Clinical Trials**

Not applicable.

5.3.9. **Additional Safety Explorations**

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

Not applicable.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

5.3.10. **Safety in the Post-market Setting**

Safety Concerns Identified Through Post-market Experience

Not applicable.

Expectations on Safety in the Post-market Setting

Not applicable.

5.3.11. **Integrated Assessment of Safety**

Overall, the rate of TEAEs reported during trial LVSOS-1-19094 was low. During the trial, no deaths, serious adverse events, TEAEs leading to treatment discontinuation, or severe adverse events were reported. A total of 11 (30%) subjects reported 17 TEAEs during the trial: 12 TEAEs occurred in 9 (27%) subjects after administration of Levothyroxine sodium oral solution compared

to 4 TEAEs in 4 (11%) subjects after administration of Synthroid [1 TEAE of blood iron decreased could not be adjudicated because clinical labs were only collected at screening and study exit (i.e., after exposure to both study drugs)].

In general, the TEAEs observed during the trial were consistent with the adverse reactions that are currently listed in Section 6 of the levothyroxine label, and no new safety findings were observed.

In conclusion, no new safety findings were observed during the trial, and the safety profile of Levothyroxine sodium oral solution remains favorable.

5.4. Statistical Issues

Not applicable.

5.5. Conclusions and Recommendations

Trial LVSOS-1-19094 established bioequivalence between Levothyroxine sodium oral solution and Synthroid per criteria established in the FDA Guidance for Industry [Draft Guidance on Levothyroxine Sodium[9]]. For a detailed review of the bioequivalence data from Trial LVSOS-1-19094, refer to the review by the clinical pharmacology reviewer, Sze W Lau, RPh, PhD. No new safety findings were observed during this trial, and the safety profile of Levothyroxine sodium oral solution is favorable. I recommend approval of the current supplement.

6. Advisory Committee Meeting and Other External Consultations

Not applicable.

7. Pediatrics

This application does not trigger the Pediatric Research Equity Act (PREA), as the proposed product is not for a new indication, new dosage form (i.e., other levothyroxine oral solutions exist and are FDA-approved), new dosing regimen, or new route of administration, and does not contain new active ingredients.

[9] Draft Guidance on Levothyroxine Sodium, December 2014

8. Labeling Recommendations

8.1. Prescription Drug Labeling

General Principles of Dosing

During the review, the Division of Medical Error Prevention and Analysis (DMEPA) noted that the proposed labeling did not contain the information regarding the volume to administer that would correspond to the microgram dose of Levothyroxine sodium oral solution. On 12/3/2021, DMEPA submitted an IR to the Applicant requesting clarification of the information regarding the volume to administer for each corresponding microgram dose of Levothyroxine sodium oral solution in order to mitigate the potential risk associated with providing a dose that does not correspond to the available syringes graduations.

In response, the Applicant proposed to revise section 2.2. General Principles of Dosing of the Prescribing Information (PI), to include a general formula on how to reach a respective volume based on the microgram dose of Levothyroxine sodium oral solution required [i.e., Dosage (mcg)/30 = Dosage (mL)], as well as information about rounding a dose up or down to the nearest syringe graduation (i.e., 0.1 mL for doses up to 5 mL or 0.2 mL for doses over 5 mL), as summarized in Table 7. This approach was found to be acceptable by DMEPA and the clinical review team. Subsequently, the Applicant submitted an updated PI with the appropriate changes to the Dosage and Administration section of the label.

Table 7. Dosing volumes in mL for the equivalent mcg dosages

Dose (meg)	Dose (mL) using 5 mL syringe	Dose (mL) using 10 mL syringe
12.5	0.4	n/a
25	0.8	n/a
50	1.7	n/a
75	2.5	n/a
88	2.9	n/a
100	3.3	n/a
112	3.7	n/a
125	4.2	n/a
137	4.6	n/a
150	5.0	n/a
175	n/a	5.8
200	n/a	6.6

300	n'a	10.0

Source: Applicant's response to IR, dated 12/22/2021

9. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

10. Postmarketing Requirements and Commitments

Not applicable.

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/s/

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