CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215809Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Addendum/Correction to Cross-Discipline Team Leader Review

ERMEZA is considered a drug-device combination product by FDA because the levothyroxine oral solution is co-packaged with standard 5 mL and 10 mL syringes for dose administration. Use of the 5 mL and 10 mL standard syringes for product administration is adequately outlined in the Prescribing Information for ERMEZA. The syringes are graduated in order to accurately measure the prescribed dose.

Specifically, the co-packaged syringes are considered a liquid medication dispenser device per 21 CFR 880.6430, thus ERMEZA meets the definition of a Part 3 combination product because it consists of a drug (levothyroxine sodium) co-packaged with a device (oral syringes). This type of combination product is coded as a Type 1- Convenience Kit or Co-Package on the 356h form. A consult from the Center for Devices and Radiological Health (CDRH) is not necessary for this oral dosing device per the CDER-CDHR MOU, given that there is nothing unique about the 5 mL and 10 mL syringes.

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/s/

SHANNON D SULLIVAN
04/29/2022 08:33:20 AM

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04/29/2022 08:37:12 AM

Cross-Discipline Team Leader Review

Date	March 31, 2022
From	Shannon Sullivan, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 215809
Applicant	Mylan Pharmaceuticals, Inc.
Date of Submission	June 30, 2021
PDUFA Goal Date	April 29, 2022
Proprietary Name	ERMEZA
Established or Proper Name	Levothyroxine sodium oral solution
Dosage Form(s)	oral solution; 150 mcg per 5 mL (30 mcg per mL)
Applicant Proposed Indication(s)/Population(s)	As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism Pituitary TSH suppression; As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer
Applicant Proposed Dosing Regimen(s)	The dosing regimen 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 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.
Recommendation on Regulatory Action	***Approval***
Recommended Indication(s)/Population(s) (if applicable)	As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism. Pituitary TSH suppression; As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.
Recommended Dosing Regimen(s) (if applicable)	Same as proposed above

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

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, and dry skin. Hypothyroidism is a serious condition, and if left untreated, it can advance to myxedema coma, a state of severely decompensated hypothyroidism that results in multiple organ damage and death.

Levothyroxine is the standard of care for the treatment of hypothyroidism. The primary goals of treatment are to normalize thyroid hormone levels and to avoid overtreatment. The starting dose of levothyroxine should be individualized, taking into account the patient's body weight, etiology of hypothyroidism, age, degree of thyroid hormone deficiency, pregnancy status, and other risk factors such as presence of cardiac disease.

Currently, multiple levothyroxine products have been approved in the U.S. for the treatment of hypothyroidism. The majority of approved levothyroxine products are oral tablet formulations. The proposed product, an oral solution formulation, provides an additional dosing option for patients who may have difficulties swallowing tablets (e.g., children, the elderly) and for whom an oral solution may be preferable or needed.

Levothyroxine is a narrow therapeutic index (NTI) drug, thus small variations in blood thyroid hormone concentrations, which can occur with use of a drug product of a different potency or bioavailability, can either lead to over-treatment or inadequate treatment. Over-treatment may cause iatrogenic thyrotoxicosis and its associated symptoms, whereas inadequate treatment can lead to worsening signs and symptoms of hypothyroidism.

In this 505(b)(2) application, the Applicant is seeking approval of Levothyroxine Sodium Oral Solution, relying on the Agency's finding of safety and effectiveness of Synthroid (NDA 021402). This oral solution formulation could provide an additional dosing option for patients with hypothyroidism. To establish bioequivalence (BE), the Applicant submitted data from one trial performed in healthy volunteers (Study LVOS-1-1994). This study established bioequivalence between the Applicant's Levothyroxine Sodium Oral Solution 150 μg/5 mL and AbbVie's Synthroid Tablets following a single oral 600 μg dose (20 mL × 150 μg/5 mL Levothyroxine Sodium Oral Solution or 2 × 300 μg Synthroid tablets) administered under fasting conditions. The data from this trial were reviewed by the clinical pharmacology reviewer, S.W. Johnny Lau, RPh, PhD, who confirmed that bioequivalence was established. No new safety findings were observed during this trial. The benefit-risk profile of the Applicant's Levothyroxine Oral Solution is favorable and the Applicant has adequately demonstrated BE between Levothyroxine Oral Solution and Synthroid.

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. • Untreated hypothyroidism can advance to myxedema coma, a state of severely decompensated hypothyroidism that results in multiple organ damage 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 is the standard of care treatment for patients with hypothyroidism. • Levothyroxine is a narrow therapeutic index drug. Small variations in thyroid hormone levels, which can occur upon substitution to a drug product of a different potency or bioavailability, can lead to either over-treatment or inadequate treatment. • The goals of treatment are to normalize thyroid hormone concentrations and to avoid overtreatment. • The proposed Levothyroxine Sodium Oral Solution provides an additional dosing option for patients who may have difficulties swallowing tablets (e.g., children, the elderly) and who thus may prefer an oral solution, which ultimately could improve compliance and overall control of thyroid hormone levels in these patients.	Levothyroxine is the standard of care for the treatment of hypothyroidism and is considered a narrow therapeutic index drug. The proposed Levothyroxine Sodium Oral Solution provides an additional dosing option for patients with hypothyroidism.
Benefit	• Expected 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, and avoidance of the severely decompensated state of myxedema coma.	Treatment of patients with hypothyroidism with levothyroxine results in improvements in the signs and symptoms of hypothyroidism, and prevention of serious consequences that may result from myxedema coma.
Risk and Risk Management	• Overall, levothyroxine therapy is well tolerated. • Adverse events typically occur due to over-treatment and are consistent with signs and symptoms of hyperthyroidism, such as tachycardia, increased blood pressure, nervousness, diarrhea, 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, including Levothyroxine Oral Solution.

2. Background

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, and dry skin. Hypothyroidism is a serious condition, and if left untreated, can advance to myxedema coma, a state of severely decompensated hypothyroidism that results in multiple organ damage and even death. In the United States, the prevalence of hypothyroidism in individuals aged 12 and older is estimated to be between 0.3% and 9.5%.[1,2,3,4] Levothyroxine is a narrow therapeutic index (NTI) drug.[5] Thus, small variations in the blood thyroid hormone concentrations, which can occur with use of a drug product of a different potency or bioavailability, can lead to either over-treatment or inadequate treatment. The current armamentarium of products approved in the U.S. to treat hypothyroidism includes multiple levothyroxine and liothyronine drugs.

In this NDA, the Applicant (Mylan Pharmaceuticals, Inc.) is seeking approval for a new Levothyroxine Oral Solution, using Synthroid (NDA 021402, approved 2002, AbbieVie) as the listed drug (LD).

Regulatory History:

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

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.

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[1]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.

[2]Canaris GJ et. al. The Colorado thyroid disease prevalence study. *Archives of Internal Medicine.* 2000; 160:526-534.

[3]Sawin CT et. al. The aging thyroid. Thyroid deficiency in the Framingham Study. *Archives of Internal Medicine.* 1985;145:1386-1388.

[4]Vanderpump MP, et. al. Epidemiology and prevention of clinical and subclinical hypothyroidism. *Thyroid.* 2002;12:839-847.

[5]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.

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 August 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 a future NDA submission, for which the Division provided written responses (see final written responses dated 11/4/2019 in DARRTS).

On January 20, 2020, TAP Pharmaceuticals AG transferred ownership of Levothyroxine Oral Solution to Mylan Pharmaceuticals, Inc (Mylan, the current Applicant).

(b) (4)

On June 30, 2021, Mylan Pharmaceuticals submitted a New Drug Application (NDA) for Levothyroxine Sodium Oral Solution 150 mcg/5mL under section 505(b)(2) 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 rationale for approval of this 505(b)(2) application (i.e., the pharmacokinetic bridge between the proposed drug product and the LD) was reviewed by the 505(b)(2) Review Committee and found to be acceptable on March 18, 2022. The proposed proprietary name, ERMEZA, was determined to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

3. Product Quality

Overall Conclusions Regarding Product Quality

The Chemistries, Manufacturing and Controls (CMC) review team concluded that the Quality data submitted in the NDA are adequate to support approval of Levothyroxine Oral Solution. In addition, the Applicant's request for Categorical Exclusion from Environmental Assessment was determined to be acceptable and was granted by the CMC review team (refer to CMC review dated March 15, 2022). See below for a brief discussion of the adequacy of the Quality data submitted regarding the Drug Product, Drug

Substance, glycerol content of the product, and Office of Process Manufacturing Assessment for NDA 215809.

Drug Substance
The drug substance is manufactured by (b) (4); the applicant referenced (b) (4) Type II DMF (b) (4) for all chemistry, manufacturing, and controls (CMC) information related to the drug substance, levothyroxine sodium USP. The CMC review team determined that the DMF, along with the additional CMC data related to Drug Substance included in the NDA, are sufficient to support approval of the proposed product.

Drug Product
The microbiology and drug product reviewers determined that the data submitted regarding the drug product (DP)—including DP composition, appearance, pH, impurities, microbiological contamination, excipient information, analytical methods, container closure system (including deliverable volume and uniformity of dosage units), dosing syringe information, compatibility information, stability data, and environmental assessment (EA)—are sufficient for approval. Excipients proposed for use in the product are present at or below the levels present in the listed drug. The CMC review team granted an exemption for environmental assessment (EA) per 21 CFR 25.31.

Based on available stability data, an expiration period of 24 months and an in-use period of 90 days after first opening were granted for the product when stored at 20°C to 25°C (68°F to 77°F) in commercial packaging.

The drug product manufacturing process and the packaging system used to manufacture the drug product used in stability and BE studies was the same as that proposed for commercial use.

Glycerol content in the proposed product
The Department of Pediatrics and Maternal Health (DPMH) identified the glycerol content of this product as a potential safety concern in neonates and infants with hypothyroidism who require chronic daily therapy. While glycerol is Generally Recognized as Safe (GRAS) by the Agency as an additive to food and drug products in amounts up to 31 grams per day, there is a theoretical and potentially dose-dependent safety concern due to the hyperosmolar effects of glycerol exposure, particularly in neonates, in whom ingestion of high quantities could result in nausea, vomiting, diarrhea, and/or dehydration due to excessive osmotic diuresis.

The glycerol (glycerin) content of this levothyroxine oral solution product is (b) (4). This exceeds the European Food Safety Authority's (EFSA) estimate of glycerol exposure from natural sources in children of 460 mg/kg. Of note, the glycerol content in this product is within the ranges seen in other oral levothyroxine solutions that are approved down to birth.

Consistent with other products approved for pediatric use down to birth that provide similar or higher glycerol content compared to ERMEZA, including other approved oral

solution levothyroxine products, the potential risks associated with ingestion of high quantities of glycerol in the younger pediatric age groups can be adequately mitigated through labeling, which was appropriately included in labeling provided by the Applicant in Section 8.4 (*Use in Specific Populations—Pediatric Use):*

> *Glycerol has the potential to cause gastrointestinal irritation resulting in vomiting and/or osmotic diarrhea. Patients in the first 3 months of life may be particularly susceptible to serious fluid and electrolyte complications from glycerol-induced gastrointestinal irritation. Closely monitor patients from birth to 3 months of age receiving ERMEZA for signs and symptoms of gastrointestinal irritation.*

DPMH agrees that this language should be retained in the final product labeling for ERMEZA.

Office of Process Manufacturing Assessment (OPMA)
The Office of Process Manufacturing Assessment (OPMA) review team concluded that the process and facility information included in the NDA are adequate because all manufacturing facilities listed in the NDA had recent inspections and were assessed as 'Approve Facility.' Therefore, the overall manufacturing inspection recommendation (OMIR) from the OPMA is approve.

4. Nonclinical Pharmacology/Toxicology

No non-clinical data were submitted nor necessary to support this 505(b)(2) NDA, given that the non-clinical pharmacological effects of levothyroxine are well established.

5. Clinical Pharmacology

The Applicant performed a pivotal bioequivalence (BE) study (Study LVOS-1-19094) between Levothyroxine Sodium Oral Solution 150 µg/5 mL and Synthroid Tablets following a single oral 600 µg dose (20 mL × 150 µg/5 mL Levothyroxine Oral Solution or 2 × 300 µg Synthroid tablets) administered under fasting conditions according to the FDA Draft Guidance on Levothyroxine Sodium.[6] Trial LVOS-1-19094 was an open-label, single-dose, randomized, two-treatment, two-period, crossover trial in 36 healthy male and female subjects with a primary objective to establish the bioequivalence of Levothyroxine Sodium Oral Solution 150 mcg/5 mL and Synthroid (levothyroxine sodium) tablets.

In each treatment 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, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18, 24 and 48 hours for levothyroxine PK characterization. There was a 35-day wash-out period between

[6]Draft Guidance on Levothyroxine Sodium:
https://www.accessdata fda.gov/drugsatfda_docs/psg/Levothyroxine_Sodium%20capsules_NDA%20021924_RC%20Oct%202018.pdf

treatment periods. The baseline PK endpoints were calculated using the average of three pre-dose concentrations (i.e., -0.5, -0.25 and 0 hour). The post-dose concentration-time profiles were adjusted by the baseline concentrations. The primary PK endpoints (i.e., C_{max} and AUC_{0-48}) were estimated using conventional non-compartmental analysis.

The levothyroxine baseline-adjusted Test to Reference ratios and corresponding 90% confidence intervals for C_{max} and AUC_{0-48} were within the bioequivalence ranges of 80-125%. Additionally, the upper limit of the 90% confidence intervals of the ratio of the within-subject standard deviation of Test product to Reference product for C_{max} and AUC_{0-48} were $\leq$2.5. Hence, bioequivalence between Levothyroxine Oral Solution and Synthroid was established.

The data from Study LVOS-1-19094 were reviewed by the Clinical Pharmacology reviewer, Dr. S.W. Lau, who confirmed the validity of the Applicant's analyses and concluded that bioequivalence between Levothyroxine Oral Solution (Test) and Synthroid tablets (Reference) was demonstrated (see Clinical Pharmacology review dated 3/14/2022).

6. Clinical/Statistical- Efficacy

No clinical efficacy data were submitted or necessary to support this 505(b)(2) application.

7. Safety

A total of 36 healthy adult subjects were enrolled in the pivotal bioequivalence study LVOS-1-19094, of whom 33 (92%) subjects received 1 dose of Levothyroxine Sodium Oral Solution and 35 (97%) subjects received 1 dose of Synthroid. Safety assessments included vital signs measurements, clinical laboratory tests (hematology, general biochemistries including liver function tests, TSH, and free T4), electrocardiograms (ECG) and recording of adverse events. There were no deaths, serious adverse events (AEs), severe AEs, or treatment-emergent AEs (TEAEs) leading to treatment discontinuation during the trial. All TEAEs observed during the study were consistent with the adverse reactions that are currently listed in the levothyroxine product labels and were similar after dosing with Levothyroxine Oral Solution and Synthroid. No new safety signals were observed (see Clinical Review by Dr. Geanina Popoveniuc, dated 3/22/2022).

8. Advisory Committee Meeting

Not applicable

9. Pediatrics

This application does not trigger the Pediatric Research and Equity Act (PREA), given that the proposed product is not a new active ingredient, new dosage form (i.e., other levothyroxine oral solutions exist and are FDA-approved), new dosing regimen, or new

route of administration, and is not intended for use for a new indication, compared to the listed drug.

10. Labeling

During the review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) noted that the proposed labeling did not contain adequate information regarding the volume of Levothyroxine Oral Solution to be administered for each corresponding microgram dosage. On 12/3/2021, DMEPA submitted an Information Request (IR) to the Applicant requesting that this information be clearly added to Section 2.2. Dosage and Administration of the Prescribing Information (PI) in order to mitigate the risk of inacurrate dosing. In response, The Applicant submitted a revised PI that included a table in Section 2.2. showing the respective volumes of Levothyroxine Oral Solution for each microgram dosage of levothyroxine. This approach was found to be acceptable by DMEPA and the clinical review team.

Additional final labeling negotiations were ongoing at the time of completion of this review.

11. Postmarketing Recommendations

None

12. CDTL Conclusions and Final Recommendation

The data provided from Study LVOS-1-19094 support approval of the Applicant's Levothyroxine Oral Solution because: 1) Synthroid, the Listed Drug, is approved as safe and effective; 2) Levothyroxine Oral Solution is pharmaceutically equivalent to Synthroid (i.e., contains the same amount of active drug and the same route of administration); 3) Levothyroxine Oral Solution is bioequivalent to Synthroid based on the results of Study LVOS-1-19094; 4) Levothyroxine Oral Solution product labeling is adequate; and 5) Levothyroxine Oral Solution is manufactured in compliance with current Good Manufacturing Practice regulations.

Therefore, I recommend **APPROVAL** of NDA 215809.

13. Recommended Comments to the Applicant

None

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/s/

SHANNON D SULLIVAN
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