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APPLICATION NUMBER:

214047Orig1s000

CLINICAL REVIEW(S)

Clinical Team Leader Memorandum

Date: November 24, 2020

From: Shannon Sullivan, M.D., PhD, Team Leader, Division of General Endocrinology (DGE)

Subject: Recommendation for approval of NDA 214047, levothyroxine sodium oral solution 100 mcg/5 mL (Thyquidity) for treatment of hypothyroidism and pituitary TSH suppression.

Introduction and Regulatory Background:

On January 31, 2020, EMP Levo US B.V. (Applicant) submitted a New Drug Application (NDA) for levothyroxine sodium oral solution 100 mcg/5 mL 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 proposed proprietary name, THYQUIDITY, was determined to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

In November of 2015, the Applicant submitted a Type B Pre-IND (PIND) meeting request for Written Responses Only (WRO) under PIND 127792, seeking guidance on the appropriate regulatory pathway; drug-device combination product design; chemistry, manufacturing, and control (CMC) issues; and the design and conduct of non-clinical and clinical studies. In August of 2017, November of 2018, and November of 2019, the Applicant requested three additional Type C meetings seeking further guidance regarding the design of their proposed bioequivalence study, the CMC data required for a future NDA submission, and human factors validation of the proposed drug-device delivery system, for which the Division provided WRO.

This memorandum includes a brief clinical review of the application and will discuss the basis for my recommendation to approve this NDA.

Basis for Approval:

To support this 505(b)(2) application, the applicant is relying upon the FDA's previous findings of safety and efficacy for the listed drug (LD), Synthroid tablets (NDA 021402). The proposed product has the same active ingredient as the LD but differs from the LD in the excipients and in its presentation as a liquid formulation.

Study EMP-P2-777: *Single Dose Crossover Comparative Bioavailability Study of Levothyroxine Oral Solution and Tablets in Healthy Male and Female Volunteers Following the Administration of a 600 µg Dose in the Fasting State:*

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

The Applicant performed a pivotal comparative bioavailability study using a single 600 mcg dose of levothyroxine sodium 100 mcg/5 mL oral solution ("Test" product) and a single 600 mcg dose of the listed drug (two Synthroid 300 mcg tablets) ("Reference" product). The standard PK criteria for bioequivalence were applied as per FDA Draft Guidance on Levothyroxine Sodium (2014)[i] and FDA Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing (2000).[ii] Baseline-adjusted AUC_{0-72} and C_{max} of the proposed product compared to the listed drug were within the bioequivalence limits of 80.00% to 125.00% (Figure 1). Therefore, the bioequivalence requirements between levothyroxine oral solution and Synthroid tablets were adequately met (*see Clinical Pharmacology review by Johnny Lau for complete details of the PK bridging study*).

Figure 1. Summary of Statistical Analysis of Baseline-Adjusted Levothyroxine between Test (Levothyroxine oral solution) and Reference (Synthroid tablets)

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS	
		TEST (n=42)[b]	REFERENCE (n=42)[b]		LOWER	UPPER
C_{max}	16.4	71.7	66.4	107.93	101.65	114.60
AUC_{0-72}	21.8	2527.1	2317.3	109.05	100.60	118.21

[a] units are in ng/mL for C_{max} and ng·h/mL for AUC_{0-72}
[b] n=41 for AUC_{0-72}
Source: EMP-P2-777 clinical study report Appendix 16.2.6.1.3

Safety in comparative BE study: A total of 44 healthy adults aged 18-45 years were randomized, of which 42 subjects (96%) received a single dose of the Test drug and 44 subjects (100%) received a single dose of the Reference product. The two subjects who did not receive the Test product discontinued from the study for reasons unrelated to any treatment emergent adverse events (TEAEs). The most common adverse events reported and considered related to study drug or study procedures (e.g., indwelling catheter insertion for blood draws) included headache, dizziness, facial paralysis (Bell's palsy), somnolence, catheter site bruising, throat irritation, cough, pain in extremity, nausea, and delayed menstruation. The AE profile was consistent with what is reported in Synthroid labeling.

Overall, 16 subjects (36%) reported a total of 28 TEAEs, with a similar incidence after dosing with Test versus Reference product (26% vs 18%, respectively). All TEAEs were mild (25/28, 89%) or moderate (3/28, 11%) in intensity. Eleven of the 42 subjects (26%) who received the Test product reported 16 TEAEs, the most common of which were throat irritation (3 subjects, 7%), headache (2 subjects, 5%), cough (2 subjects), dizziness (2 subjects), and injection site swelling (after indwelling catheter placement, 2 subjects). Eight of the 44 subjects (18%) who received the Reference product reported 12 TEAEs, the most common of which were headache (2 subjects, 5%) and injection site swelling (2 subjects, 5%). Most of the TEAEs were considered study drug-related [14/16 (88%) after Test dosing and 7/12 (58%) after Reference dosing, respectively]. Most TEAEs (26/28, 93%) had resolved or were resolving at the end of the study; one event of protein in the urine was lost to follow-up and 1 event of Bell's Palsy was not

resolved. There were no deaths or serious AEs during the study, and no subject was withdrawn due to an AE.

Overall, the study did not identify any new safety signals for levothyroxine and the safety findings are consistent with Synthroid labeling, which the Applicant is relying upon.

Safety of glycerol content: The glycerol (glycerin) content of this product ((b) (4) of glycerol contained in the maximum clinical dose of 300 mcg/daily) was identified by the Department of Pediatrics and Maternal Health (DPMH) as a potential safety concern in neonates and infants with hypothyroidism requiring chronic daily therapy of this product. 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.

DPMH and the Office of Pharmacology and Toxicology (OPT)-Neonatology reviewed the available data regarding glycerol safety in the neonatal population. DPMH and OPT-Neonatology determined that although there are knowledge gaps because glycerol toxicity has not been studied in juvenile animals, there are at least three drug products approved for use down to birth that provide comparable or higher glycerol exposure to neonates than the proposed levothyroxine oral solution, including the only other approved levothyroxine oral solution (Tirosint-sol, NDA 206977)(see also labeling for NDA 206356, Orfadin and NDA 203284, Ravicti).

After consultation with DPMH, OPT-Neonatology, and the Office of Surveillance and Epidemiology (OSE), the review team determined that the potential risks associated with ingestion of high quantities of glycerol in the younger pediatric age groups could be adequately mitigated through labeling. To inform prescribers and patients' caregivers of this risk, the following was added to Section 8.4 (*Use in Specific Populations—Pediatric Use)* of the product label:

> *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 THYQUIDITY for signs and symptoms of gastrointestinal irritation.*

Safety of proposed syringe with regard to medication error prevention: The Division of Medical Error Prevention and Analysis (DMEPA) was concerned about the risk for medication errors (b) (4) (b) (4) for administering this product. This proposed (b) (4) (b) (4) that were potentially confusing to users and were therefore susceptible (b) (4) (b) (4)

[redacted]. In an Information Request sent to the Applicant on June 16, 2020, DMEPA requested that the Applicant "implement risk mitigation strategies [redacted] or, alternatively, reconsider "[redacted] for the safe and effective use of your product." Based on this feedback, the Applicant decided [redacted] to allow pharmacies to dispense an appropriate, traditional oral syringe for each user. This approach was considered acceptable to DMEPA, and I agree that this is acceptable from a medication error perspective.

505(b)(2) Committee Assessment: 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 on October 20, 2020 and found to be acceptable.

Pediatric Study Plan:
The Pediatric Review Committee (PeRC) discussed this application in July of 2020 and determined that because the proposed product is not a new dosage form of levothyroxine (compared to levothyroxine oral solution, Tirosint-Sol, NDA 206977, approved 2016), the Pediatric Research and Equity Act (PREA) is *not* triggered. Therefore, it was communicated to the Applicant that a Pediatric Study Plan (PSP) would not be necessary.

Clinical TL Recommendation:
The bridge between the proposed drug product and the listed drug Synthroid was adequately established with an appropriately designed PK bridging study. No new safety signals were identified in the completed PK bioequivalence study; however, the high glycerol content of this product warrants addition to labeling regarding potential risks to neonates and infants receiving chronic therapy.

I recommend approval of NDA 214047, levothyroxine sodium oral solution (THYQUIDITY), for treatment of hypothyroidism and pituitary TSH suppression, for adult and pediatric patients down to birth, with additions to labeling regarding potential risks to the neonatal/infant population related to the high glycerol content of this oral solution.

Shannon Sullivan, MD, PhD
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[i]http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM428208.pdf.
[ii]http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071946.pdf)

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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