CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214047Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	11/27/2020
From	Jayabharathi Vaidyanathan, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 214047
Applicant	EMP Levo US B.V.
Date of Submission	1/31/2020
PDUFA Goal Date	11/30/2020
Proprietary Name / Established (USAN) names	THYQUIDITY/Levothyroxine sodium
Dosage forms / Strength	Solution; 100 mcg/5 mL
Proposed Indication(s)	To treat hypothyroidism and suppress pituitary thyrotropin-stimulating hormone (TSH) 1) hypothyroidism - as replacement therapy in congenital or acquired hypothyroidism [SNOMED CT term: 40930008, Hypothyroidism (disorder)] 2) pituitary thyrotropin-stimulating hormone (TSH) suppression - as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer [SNOMED CT term: 704078008, Thyroid stimulating hormone suppression therapy (procedure)]
Recommended Action:	Approval

1. Risk-Benefit Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

THYQUIDITY is a levothyroxine sodium oral solution where each mL of THYQUIDITY contains 20 mcg of levothyroxine sodium. The applicant is relying on FDA's findings of safety and effectiveness for Synthroid and seeks the same indications as Synthroid – to treat hypothyroidism and suppress pituitary thyroid stimulating hormone (TSH). Hypothyroidism is a common disease that occurs across the age spectrum from congenital hypothyroidism diagnosed at birth to diagnosis in older patients. Hypothyroidism can be primary due to loss of function at the thyroid gland, secondary due to loss of secretion of TSH stimulating hormone from the pituitary gland, or tertiary due to loss of thyrotropin releasing hormone (TRH) from the hypothalamus. Suppression of TSH is a primary method of treating thyroid cancer patients as an adjunct to surgery and radioiodine therapy.

The safety and effectiveness of levothyroxine therapy for the proposed indications are well understood and documented. Dosing is titrated with TSH monitoring to ensure correct doing with TSH maintained in the appropriate range.

To support the approval of THYQUIDITY for the proposed indications, the applicant submitted Study EMP-P2-777, a randomized 2-treatment, 2-period, 2-sequence, crossover, single-dose study in healthy subjects in order to determine the relative bioavailability following oral administration of the proposed levothyroxine oral solution (30 mL of 100 mcg/5mL solution) to that of the listed drug, Synthroid (600 mcg) under fasting conditions. The 90% confidence interval of the baseline-adjusted levothyroxine Cmax geometric mean ratio (GMR) and AUC0-72 GMR for 30 mL of 100 mcg/5 mL levothyroxine sodium oral solution versus two 300 mcg Synthroid oral tablets are all within the 80 – 125% bioequivalence margins under fasting conditions. Therefore, it is acceptable for the applicant to rely on FDA's findings of safety and effectiveness for Synthroid.

One formulation difference between THYQUIDITY and Synthroid is the presence of glycerol (b) (4). At the expected maximum recommended clinical dose (approximately 120 mcg in an 8 Kg child or 300 mcg in adults) the amount of glycerol administered is (b) (4) per day, respectively. 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. 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 applicant has adequately demonstrated comparability between THYQUIDITY and Synthroid with physiochemical data as well as clinical pharmacology data. It is reasonable to expect that THYQUIDITY will have the same risks and benefits as Synthroid for the indications sought. The concern regarding the glycerol content and the potential adverse gastrointestinal effects in neonates and young children treated chronically with THYQUIDITY will be labeled.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hypothyroidism is a common condition, affecting millions of patients from birth to older age groups. The underlying etiology of hypothyroidism varies. • Suppression of pituitary secretion of TSH is an adjunct to thyroidectomy and radioactive iodine therapy for treatment of thyroid cancer.	
Current Treatment Options	• There are multiple manufacturers of levothyroxine. Three dosage forms are currently available, injection, tablet and oral solution. • THYQUIDITY will be the second oral solution of levothyroxine.	This is the second oral solution formulation of levothyroxine which may be beneficial to patients, especially children, who cannot swallow tablets.
Benefit	• The applicant has adequately demonstrated comparability between THYQUIDITY and Synthroid with physiochemical data as well as clinical pharmacology data. It is reasonable to expect that THYQUIDITY will have the same benefits as Synthroid and other levothyroxine products for the indications sought.	The THYQUIDITY product labeling will be the same as that of Synthroid.
Risk and Risk Management	• The applicant has adequately demonstrated comparability between THYQUIDITY and Synthroid with physiochemical data as well as clinical pharmacology data. It is reasonable to expect that THYQUIDITY will have the same risks as Synthroid and other levothyroxine products for the indications sought. • THYQUIDITY contains (b) (4) glycerol/ml or drug product. This amount of glycerol has the potential to cause adverse gastrointestinal effects in neonates and young children treated chronically with THYQUIDITY.	The THYQUIDITY product labeling will contain the same Boxed Warning, Warnings and Precautions and Adverse Reaction labeling as Synthroid. The concern regarding adverse gastrointestinal adverse events due to the glycerol content of THYQUIDITY will be labeled under the pediatric subsection

2. Background

On January 31, 2020, EMP levo submitted NDA for THYQUIDITY (levothyroxine sodium oral solution) as a 505 (b) (2) application relying on FDA's findings of the safety and effectiveness for Synthroid (NDA 021402). THYQUIDITY is a solution provided in a multiple-dose amber glass bottle with child resistant closure. Each mL of THYQUIDITY contains 20 mcg of levothyroxine sodium. The dose will be measured and administered using a calibrated pharmacy provided oral syringe. The proposed indication is same as the listed drug – to treat hypothyroidism and suppress pituitary thyrotropin stimulating hormone (TSH).

As per the applicant, the expected advantage of an oral solution compared to a solid oral formulation of levothyroxine is the ease of administration, to patients who have difficulties to not able to swallow intact capsules or tablets (including small children).

The major regulatory interactions with the applicant and the Agency are summarized below:

- On September 25, 2018, a request that FDA grant exemption from the IND regulations, and, therefore, not require an IND to conduct the proposed investigation for levothyroxine sodium oral solution was submitted. This request was granted by the Agency on November 15, 2018.
- On October 23, 2015, a PIND meeting was requested, and written responses were granted on December 18, 2015. This meeting set the overall direction of the levothyroxine sodium oral solution development program. The Agency provided overall guidance on submission of 505(b)(2) NDA.
- 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. The Agency agreed that the comparative PK study with levothyroxine sodium oral solution and Synthroid can be conducted under fasting conditions only and provided other study design related comments.

3. Quality

The Office of Pharmaceutical Quality (OPQ) review team recommends approval for this application (see REV-QUALITY-25 (Integrated Quality Review) dated 10/21/2020 in DARRTS).

Drug substance – The review concluded that the drug substance is made with adequate quality and control. The drug substance is manufactured by (b) (4)). The applicant provided reference to (b) (4) DMF (Drug master file), for all chemistry, manufacturing and control (CMC) information related to the drug substance, levothyroxine sodium USP. It was concluded that the proposed drug substance specification is consistent with the USP monograph for levothyroxine sodium and is adequate to control the quality of

the drug substance used in the drug product manufacturing. The certificate of analysis of drug substance batches used to produce the drug product registration batches were provided in the NDA and were found to be adequate.

Drug product –THYQUIDITY is a solution provided in a multiple-dose amber glass bottle with child resistant closure. Each mL of THYQUIDITY contains 20 mcg of levothyroxine sodium. Each mL contains 20 mcg levothyroxine sodium, (b) (4) mg glycerin, (b) (4) citric acid, and (b) (4) methylparaben in purified water. Sodium hydroxide is added (b) (4) (b) (4). The composition of the proposed commercial product is the same as the one used in pilot and pivotal BE studies. The excipients used in the drug product are of compendial grade. The maximum daily dose for this product is 300 mcg per day. The maximum daily dose will contain (b) (4) glycerin. The remaining excipients are present at acceptable levels for oral doses as determined by the FDA inactive ingredients database. Refer to discussion on the glycerin content in sections below. The drug product is manufactured by (b) (4) (b) (4). The drug product specification and microbiological contamination controls of the product were found to be adequate. Based on available stability data, an expiration period of 18 months is granted for the product, when stored at 20°C to 25°C (68°F to 77°F) in commercial packaging. An in-use period of 8 weeks is granted for the product after first use. The container closure is made from materials commonly used for storing pharmaceutical products and protects the drug substance from light. A dose accuracy study with the pharmacy syringes confirmed that the deliverable volumes dispensed are acceptable.

Manufacturing process and facility – The drug product manufacturing process, and the packaging system used to manufacture the drug product used in pilot and pivotal BE studies is the same as that proposed for commercial use. The overall manufacturing inspection recommendation (OMIR) from the Office of Manufacturing Assessment (OPMA) for this NDA is for approval. The manufacturing process and Facility information in the NDA was found to be adequate.

There are no outstanding deficiencies related to OPQ review.

4. Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology reviewers recommend approval of NDA 214047 (see REV-NONCLINICAL-21 (Primary Review) dated 10/16/2020 in DARRTS).

No animal studies were conducted in support of the NDA 214047 for levothyroxine sodium oral solution. 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. All identified impurities as well as extractable/leachables were within acceptable limits. 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. 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). 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). Overall, there are no nonclinical safety concerns regarding the use of levothyroxine oral solution based on available data.

I concur with reviewer's assessment that there are no nonclinical pharmacology/toxicology issues that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The applicant's submission included the results of one relative bioavailability study, EMP-P2-777 comparing the relative bioavailability of levothyroxine sodium oral solution to the listed product. This study was an open label, randomized 2-treatment, 2-period, 2-sequence, crossover, single-dose study in healthy subjects. 30 mL of the to-be-marketed 100 mcg/5 mL levothyroxine sodium oral solution (Test) was compared to administration of two US approved 300 mcg SYNTHROID oral tablets (Reference). The tested formulation of levothyroxine sodium oral solution in the bridging study (EMP-P2-777) is identical to the to-be-marketed formulation of levothyroxine sodium oral solution.

Study EMP-P2-777 shows that the 90% confidence interval of the baseline-adjusted levothyroxine C_{max} geometric mean ratio (GMR) and AUC_{0-72} GMR for 30 mL of 100 µg/5 mL levothyroxine sodium oral solution versus two 300 µg SYNTHROID oral tablets are all within the 80 – 125% bioequivalence goalpost under fasting (see REV-CLINPHARM-21 (Primary Review) dated 10/20/2020 in DARRTS),

Table 1: Statistical comparisons of baseline-adjusted levothyroxine pharmacokinetics upon the administration of 30 mL of 100 µg/5 mL levothyroxine sodium oral solution versus the administration of two 300 µg SYNTHROID oral tablets under fasting.

Baseline-adjusted Levothyroxine Parameter	LS Geometric Means		Geometric Mean Ratio (GMR, %)	90% Confidence Interval	
	Test	Reference		Lower	Upper
C_{max} (ng/mL)	71.7	66.4	107.93	101.65	114.60
AUC_{0-72} (ng•h/mL)	2527.1	2317.3	109.05	100.60	118.21

The study results provide a bridge to reference the effectiveness and safety of THYQUIDITY to the FDA's findings of the listed product's effectiveness and safety for levothyroxine sodium oral tablets.

6. Clinical Efficacy

No new clinical efficacy studies have been conducted for this NDA. The applicant is relying on FDA's findings of effectiveness for Synthroid (NDA 021402). The results of study EMP-P2-777 indicate that THYQUIDITY is bioequivalent to Synthroid and it is therefore, reasonable to rely on Synthroid's findings of efficacy and safety.

7. Clinical Safety

For this NDA, the applicant is predominantly relying on FDA's findings of safety for Synthroid (NDA 021402). Adverse reactions reported in Synthroid product labeling are mainly related to hyperthyroidism due to hormone over-replacement and include:

General: fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating
Central nervous system: headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, insomnia
Musculoskeletal: tremors, muscle weakness, muscle spasm
Cardiovascular: palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction, cardiac arrest
Respiratory: dyspnea
Gastrointestinal: diarrhea, vomiting, abdominal cramps, elevations in liver function tests
Dermatologic: hair loss, flushing, rash
Endocrine: decreased bone mineral density
Reproductive: menstrual irregularities, impaired fertility
Seizures have been reported rarely with the institution of levothyroxine therapy.

Adverse Reactions specific to children receiving levothyroxine therapy include pseudotumor cerebri and slipped capital femoral epiphysis. Thyroid hormone overtreatment may also result in craniosynostosis in infants and premature closure of the epiphyses in children with resultant compromised adult height.

Study EMP-P2-777 enrolled 44 heathy male and female subjects for this single-center, randomized, open label, single-dose, two-period crossover study. Each subject received a single 600 mcg of thyroid hormone during each dosing period with a washout out of 35 days between dosing periods. Two subjects withdrew from the study between period 1 and period 2. One subject withdrew because of a screening sample positive for recreational drugs and the second subject withdrew consent without reporting any adverse events. Forty-two subjects completed the trial and received both thyroid hormone preparations.

There were no deaths, serious adverse events, or adverse events leading to study withdrawal reported. Adverse events were reported by 11/42 (26%) subjects while receiving THYQUIDITY and 8/44 (18% subjects while receiving Synthroid). Adverse events are outlined in the table below. The most common adverse events while receiving THYQUIDITY were throat irritation, cough, headache, and dizziness.

Table 2: Adverse Events Reported in Study EMP-P2-777

MedDRA Preferred Term	**THYQUIDITY N = 42**	**Synthroid N = 44**
At least one adverse event n (%)	11 (26)	8 (18)
Throat irritation	3 (7)	0
Cough	2 (5)	0
Headache	2 (5)	2 (5)
Dizziness	2 (5)	2 (5)
Facial paralysis	1 (2)	0
Somnolence	1 (2)	0
Pain in extremity	1 (2)	0
Menstruation delayed	1 (2)	0
Fatigue	0	1 (2)
Vessel puncture site pain	0	1 (2)
Musculoskeletal pain	0	1 (2)
Protein, urine present	0	1 (2)

Source: Table 11, page 47, emp-p2-777-clin-stud-rep

The safety data from study EMP-P2-777 are similar to those seen with Synthroid and no new safety signals are identified in this small study of healthy volunteers. It is reasonable to rely on the safety findings from Synthroid.

8. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

9. Pediatrics

The Division of General Endocrinology (DGE) consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the Pregnancy and Lactation subsections of the product's labeling. The applicant was asked to provide a review of literature on the use of levothyroxine during pregnancy, lactation, and in males and females of reproductive potential. DPMH also reviewed the glycerol content in the formulation. The review of the literature data did not show any risk due to levothyroxine use in pregnancy. Because hypothyroidism is associated with adverse pregnancy outcomes, levothyroxine replacement is necessary in pregnancy. DPMH concluded that the applicant provided an adequate review of published literature regarding levothyroxine and glycerol use in pregnancy. To support the safety of the

amount of glycerol present in levothyroxine oral solution, the applicant noted that an approved product contains a higher daily dose of glycerin (ANDA 200343). Published animal studies have not shown glycerol to be teratogenic, mutagenic or carcinogenic. Because glycerin is GRAS and the proposed daily maximum dose is within the maximum daily exposure (31g) of inactive ingredient of FDA's approved drug products and the accepted range in food and beverages by ESFU, the amount of glycerol in levothyroxine sodium oral solution is not expected to result in major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Overall, based on data regarding levothyroxine use in females of reproductive potential, in pregnancy, and in lactating women for several decades, DPMH has is no safety concern for levothyroxine or glycerol at the current time with use in pregnancy or lactation. DPMH does not recommend any postmarking study (see CONSULT-REV-DPMH-03 (Maternal Health Review) in DARRTS dated 9/2/2020).

10. Other Relevant Regulatory Issues

Office of Study Integrity and Surveillance inspection (OSIS)
OSIS recommended to accept the data without an on-site inspection based on previous inspection of the clinical and analytical sites with outcome of No Action Indicated at these sites (see CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review) in DARRTS dated 3/20/2020).

Financial Disclosure
FDA 3454 form was submitted confirming that the applicant of the submitted studies did not enter into any financial arrangement with the listed clinical investigators that could influence the outcome of the trial.

11. Labeling

Proprietary name
The proposed proprietary name for levothyroxine oral solution is THYQUIDITY. This was reviewed and deemed acceptable by the Division of Medication Error Prevention and Analysis (DMEPA). A letter stating this was issued to the applicant on 9/1/2020. DMEPA also reviewed the submitted container label and carton labeling and determined it to be acceptable from a medication error perspective (see CONSULT-REV-SAFETY-06 (Labeling review) in DARRTS dated 10/20/2020; REV-SURVEPI-33 (Proprietary Name Review) in DARRTS dated 8/27/2020).

Labeling
The labeling language is consistent with the listed drug package insert. Since THYQUIDITY contains glycerol, there is a recommendation to the applicant to inform prescribers the potential safety concern in pediatric patients in Section 8.4.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

The scientific bridge between the proposed levothyroxine sodium oral solution and the listed drug was established based on the relative bioavailability study EMP-P2-077 which showed that THYQUIDITY was bioequivalent to Synthroid tablets. Thus, reliance on the previous determination of the effectiveness and safety of the listed drug is acceptable.

- Recommendation for Post-marketing Risk Evaluation and Management Strategies

None

- Recommendation for other Post-marketing Requirements and Commitments

None

- Recommended Comments to Applicant

None

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/

JAYABHARATHI VAIDYANATHAN
11/28/2020 11:08:04 AM

THERESA E KEHOE
11/29/2020 02:05:16 PM
I concur with the regulatory decision reached and this memo will serve as the summary basis of approval