CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214047Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 26, 2020
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 214047
Product Name and Strength:	Thyquidity (levothyroxine sodium) oral solution, 100 mcg/5 mL (20 mcg/mL)
Applicant/Sponsor Name:	EMP Levo
OSE RCM #:	2020-221-1
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on October 22, 2020 for Thyquidity. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Thyquidity (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that were request by DMEPA on July 23, 2020.[a]

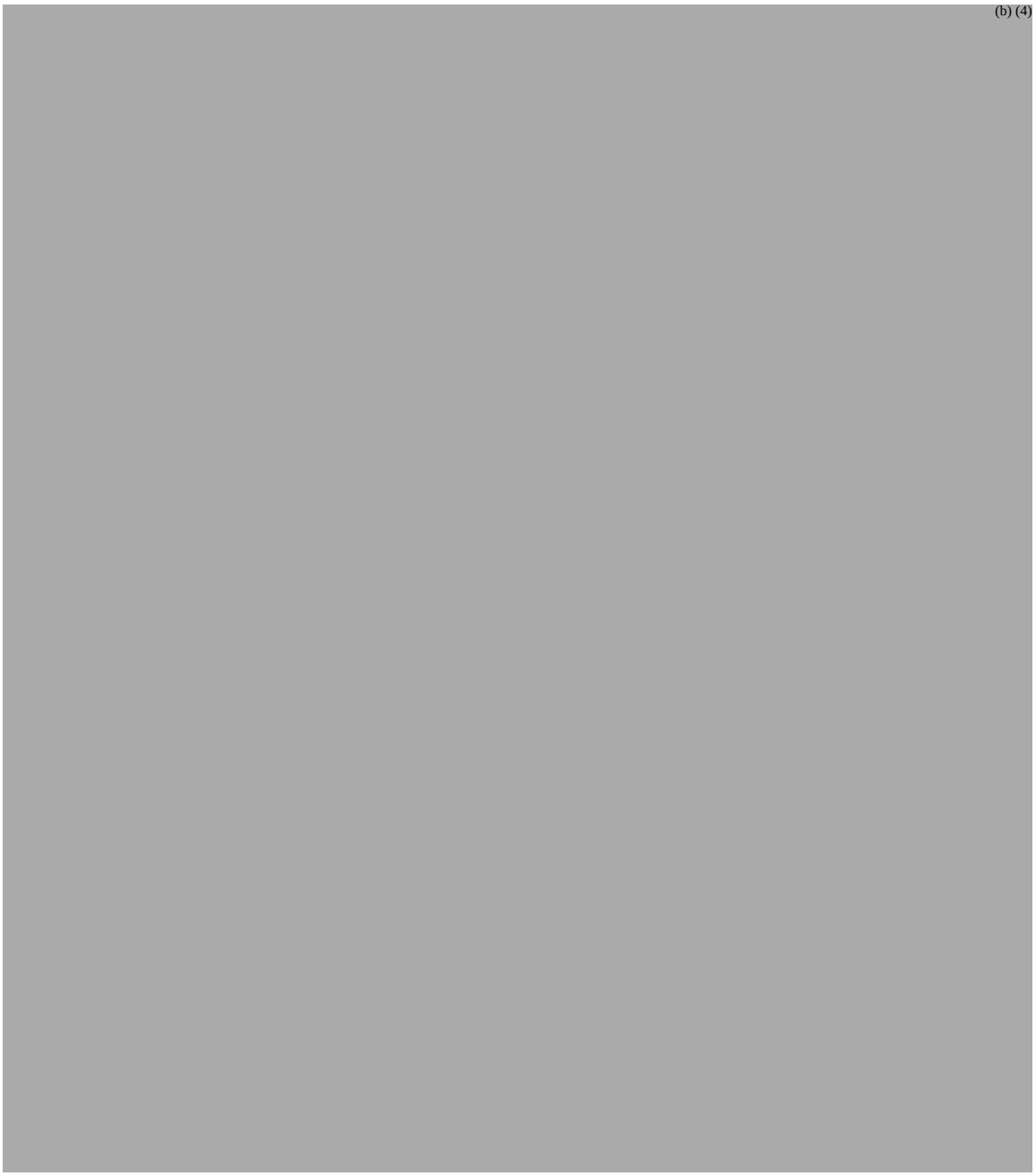
2 CONCLUSION

The Applicant implemented all of our recommendations and we do not have any additional recommendations at this time.

[a] Fanari, M. Label and Labeling Review for Thyquidity (NDA 214047). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jul 23. RCM No.: 2020-221.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 22, 2020

Container label



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/

MELINA N FANARI
10/26/2020 12:36:28 PM

SEVAN H KOLEJIAN
10/26/2020 12:43:21 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 23, 2020

To: Linda Galgay, Regulatory Project Manager
Division of General Endocrinology (DGE)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (levothyroxine sodium) oral solution

NDA: 214047

In response to DGE's consult request dated February 7, 2020, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for TRADENAME (levothyroxine sodium) oral solution.

OPDP's review of the proposed PI is based on the draft received by electronic mail from DGE (Linda Galgay) on October 21, 2020 and we have no comments at this time.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at (301) 796-4530 or Ankur.Kalola@fda.hhs.gov.

19 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

---

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/

ANKUR S KALOLA
10/23/2020 11:52:20 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 9/1/2020 **Date consulted:** 3/11/2020

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health (DPMH)

To: Division of General Endocrinology (DGE)

Drug: levothyroxine sodium oral solution

NDA: 214047

Applicant: EMP Levo US B.V.

Subject: new NDA

Indication:

- Hypothyroidism: As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.
- Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

  Limitations of Use:
  - Not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients.
  - Not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

Materials
Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 214047
- DGE consult form for DPMH, DARRTS Reference ID 4573979
- DPMH review of Levothyroxine Sodium injection, NDA 210632, by Christos Mastroyannis, MD, on March 7, 2019, DARRTS Reference ID 4400668[1]
- DPMH review of Tirosint-Sol, NDA 206977, by Jacqueline Spaulding, MD, on November 11, 2016, DARRTS Reference ID 206977[2]

Consult Question:

- DGE is seeking assistance from DPMH in developing Sections 8.1, 8.2 and 8.3 of the product's labeling.

INTRODUCTION AND BACKGROUND

On January 31, 2020, the applicant (EMP Levo US B.V.) submitted a new NDA 214047 for levothyroxine sodium oral solution for approval. The Division of General Endocrinology (DGE) consulted the Division of Pediatric and Maternal Health (DPMH) on March 11, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Levothyroxine sodium was first synthesized in 1927 and initially approved August 21, 2000 in United States as Unithroid oral tablet, indicated for hypothyroidism and pituitary TSH suppression.
- On January 31, 2020, EMP Levo US B.V. submitted a new formulation for levothyroxine sodium oral solution, NDA 214047, for the indications below:
    - Hypothyroidism: As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.
    - Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.
- This approval is based on 505(b)(2) regulatory pathway of the Federal Food, Drug, and Cosmetic, which relies on the Agency's previous finding of safety and effectiveness of the reference listed drug (RLD), Synthroid (levothyroxine sodium) tablets, for oral use (NDA 021402), approved July 24, 2002.
- On April 17, 2020, an information request (IR) was sent by FDA to the applicant to obtain a review of literature on the use of levothyroxine during pregnancy, lactation, and in males and females of reproductive potential.
- On April 30, 2020, the applicant replied to the IR with a Labeling Supplement.

[1] The Levothyroxine Sodium injection review was part of the materials reviewed to avoid duplicating background information and literature relevant to the underlying medical condition but was not a source relied upon for the labeling recommendations below.

[2] The Tirosint-Sol review was part of the materials reviewed to avoid duplicating background information and literature relevant to the underlying medical condition but was not a source relied upon for the labeling recommendations below.

Drug Characteristics

Levothyroxine Sodium Oral Solution, 100 mcg/5mL, is a product consisting of an aqueous solution of 100mcg levothyroxine sodium per 5mL. It contains glycerol, an inactive ingredient. At the expected maximum clinical dose of 300 mcg/day, levothyroxine sodium oral solution contains (b) (4) glycerol. Exposure to this amount of glycerol is not qualified by prior use in a U.S.-approved product intended for oral administration. Therefore, current review will provide a review of glycerol as well as levothyroxine.

Levothyroxine Characteristics

Drug Class	Thyroid hormone
Mechanism of action	-Thyroid hormones exert their physiologic actions through control of DNA transcription and protein synthesis. Triiodothyronine (T3) and L-thyroxine (T4) diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins. -The physiological actions of thyroid hormones are produced predominantly by T3, the majority of which (approximately 80%) is derived from T4 by deiodination in peripheral tissues.
Molecular weight	798.85 g/mol
Half-life	6-7 days
Protein Binding	99%
Bioavailability	40-80%
Serious Adverse Reactions in current labeling	Over treatment may cause cardiac adverse reactions in the elderly and in patients with underlying cardiovascular disease.

Glycerol Characteristics

Drug Class	a simple polyol compound
Mechanism of action	N/A
Molecular weight	92.1 g/mol
Half-life	30-45 min
Protein Binding	N/A
Bioavailability	N/A
Adverse Reactions[3]	Arrhythmias, confusion, dizziness, headache, dehydration, hyperglycemia, polydipsia, cramping pain, diarrhea, dry mouth, nausea, rectal irritation, tenesmus, vomiting.

Current State of the Labeling for the approved RLD, Synthroid tablets

- Approved labeling is in the PLLR format.
- There is a boxed warning for this drug.
    - Thyroid hormones, including SYNTHROID should not be used for the treatment of obesity or for weight loss.

[3] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 3/16/2020.

- Doses beyond the range of daily hormonal requirements may produce serious or even life-threatening manifestations of toxicity.

- There is a contraindication for use of Synthroid in those with uncorrected adrenal insufficiency.

Subsection 8.1 Pregnancy notes the following:

"Experience with levothyroxine use in pregnant women, including data from post-marketing studies, have not reported increased rates of major birth defects or miscarriages. There are risks to the mother and fetus associated with untreated hypothyroidism in pregnancy. Since TSH levels may increase during pregnancy, TSH should be monitored and SYNTHROID dosage adjusted during pregnancy There are no animal studies conducted with levothyroxine during pregnancy. SYNTHROID should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated."

Subsection 8.2 Lactation notes the following:

"Limited published studies report that levothyroxine is present in human milk. However, there is insufficient information to determine the effects of levothyroxine on the breastfed infant and no available information on the effects of levothyroxine on milk production. Adequate levothyroxine treatment during lactation may normalize milk production in hypothyroid lactating mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SYNTHROID and any potential adverse effects on the breastfed infant from SYNTHROID or from the underlying maternal condition."

- There are no existing pregnancy testing/contraception recommendations.
- There are known drug-drug interactions with hormonal contraceptives. Subsection 7.1 notes estrogens and estrogen-containing oral contraceptives may increase the serum thyroxine-binding globulin (TBG) concentration, therefore may alter T4 and T3 serum transport without effecting free T4 concentration.

REVIEW

PREGNANCY

Condition: Hypothyroidism and pregnancy[4,5,6]

- *Prevalence*: The prevalence of gestational hypothyroidism (overt and subclinical) is 2 to 5%. Overt hypothyroidism complicates 2 to 10 per 1000 pregnancies.
- *Cause*: In Western countries, the most common cause of primary hypothyroidism is autoimmune thyroiditis. In other parts of the world, iodine deficiency still remains an important factor. Other causes include: thyroidectomy, radioiodine therapy, and drugs, such as amiodarone, lithium, ethionamide, iodine, interferon, sunitinib, rifampicin, and thalidomide.
- *Clinical features*: tiredness, weight gain, dry skin, cold intolerance, constipation, muscle weakness, puffiness around the eyes, hoarse voice, and poor memory.
- *Physiology:*

[4] ACOG Practice Bulletin: Thyroids Disease in Pregnancy, 2015.

[5] Tosun G., Kose S., İşbilen Başok B., Altunyurt S. First-trimester placental function in levothyroxine-using pregnant women: a case-control study. Gynecological Endocrinology 2020 36:3 (233-237)

[6] DPMH review of NDA 206977 on November 11, 2011, DARRTS Reference ID 206977

    - Maternal T4 is transferred to the fetus throughout the entire pregnancy and is important for normal fetal brain development. It is especially important before the fetal thyroid gland begins concentrating iodine and synthesizing thyroid hormone at approximately 12 weeks of gestation.
    - Pregnancy is associated with an increased T4 requirement in approximately one third of supplemented women. This is believed to be related to an increase estrogen production. There is also an anticipated increase in T4 requirements in those without T4 reserve, including patients with a history of ablation or thyroidectomy.
- *Effect on Pregnancy:*
    - Overt, untreated maternal hypothyroidism has been associated with an increased risk of low birth weight and impaired neuropsychologic development of the offspring. Fetal goiter, as result of maternal thyroid inhibitor antibodies crossing the placenta, is rare.
    - Overt hypothyroidism has also been linked to some adverse pregnancy outcomes, such as spontaneous abortion, low birth weight, preterm delivery, gestational hypertension, preeclampsia, placental abruption, fetal loss, and postpartum hemorrhage.
    - Significant changes in placental function markers have been observed in euthyroid levothyroxine-using pregnant women during the first trimester. The frequency of obstetric complications does not appear to be dose dependent. Tosun et al.[5] suggest that differences still exist in hypothyroid women who are fully corrected with thyroid hormone compared to women without thyroid disorder.
- *Published treatment guidelines during pregnancy:*
    - Testing in pregnancy: TSH and free T4 should be measured in pregnancy and followed. T3 and antithyroid antibody can be considered.
    - The American Thyroid Association and the American Association of Clinical Endocrinologists recommend thyroid hormone replacement in the dosage of 1-2 μg/kg/day or approximately 100 μg daily to minimize the risk of adverse outcomes is recommended. The dose should be adjusted based on TSH level every 4 to 6 weeks. The levothyroxine dose is adjusted by 25 μg to 50 μg increments until TSH values are normal (<2.5 mIU/L).
    - According to ACOG Practice Bulletin in 2015, thyroid hormone replacement is not recommended in treatment of subclinical hypothyroidism in pregnancy, because there is no evidence that treatment in pregnancy improves pregnancy outcomes, such as preterm birth, abruption, preeclampsia, gestational diabetes, admission to neonatal intensive care unit and neurocognitive development.

Nonclinical Experience

Animal reproduction studies have not been conducted with levothyroxine. There are no nonclinical pharmacology or toxicology studies provided with the submission.

Review of Clinical Trials

Since the application was submitted under 505(b)(2) pathway, the applicant is relying on the Agency's finding of safety and effectiveness for NDA 021402. The applicant only submitted two

clinical studies to compare the bioavailability of the oral solution formulation to that of the already marketed tablet formulation of levothyroxine in healthy volunteers. No pregnant women were present in either studies.

Review of Literature

Applicant's Review of Literature

The applicant conducted an online search of published literature in PubMed and google regarding the use of levothyroxine in pregnancy as well as the use of glycerol in pregnancy. The applicant found several relevant publications regarding the use of thyroid hormone in pregnancy and no information regarding the use of glycerol in pregnancy. For a full account of applicant's submission of review of literature in pregnancy, see applicant's submission on April 30, 2020, Module 1.11, under "Response to Maternal Health Information Request" (sequence number 005).

The applicant concluded:

> [These] data support the proposed labeling information in section 8.1 Pregnancy, which is indeed the information included in the reference listed drug (RLD, Synthroid®) label.

In regard to glycerol, the applicant noted that an approved product contains a higher daily dose of glycerin (ANDA 200343).

Product Name	**Ingredient**	**Quantity (mg/mL)**	**MDD**	**MDI of ingredient**
Levothyroxine Sodium Oral Solution, 100 mcg/5 mL (NDA 214047)	Glycerol (Glycerin)	(b) (4)	300 mcg (15 mL)	(b) (4)
Hydrocodone Bitartrate and Acetaminophen Oral Solution, 7.5 mg/325 mg per 15 mL (ANDA 200343)			90 mL	

Applicant's table.

Reviewer comment:

The DGE Chemistry and Pharmacology Toxicology teams reviewed the applicant's submission and agreed that the glycerol component quantity in levothyroxine sodium oral solution is safe for oral use.

DPMH's Review of Literature

Levothyroxine

In the 2019 DPMH review of levothyroxine by Christos Mastroyannis, MD,[7] DPMH noted:

> "Treatment of hypothyroidism in pregnancy is recommended because it is associated with complications to the mother and the fetus. "There is no evidence based on DPMH's review of the available data that levothyroxine use in pregnant women is associated with a risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes."

[7] DPMH review of NDA 210632 by Christos Mastroyannis, MD, on March 7, 2019, DARRTS Reference ID 4400668

See APPENDIX A for a summary of previous DPMH reviewed literature of the use of levothyroxine in pregnancy.

DPMH conducted an updated published literature review, since 2019, using Embase, Pubmed, Micromedex,[3] ReproTox,[8] TERIS,[9] and Shepard's.[10] Search terms used were "levothyroxine" AND "pregnancy," "levothyroxine" AND "pregnancy" AND "fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage." There are several relevant studies. See Appendix B for a tabulated list of relevant published literature of the use of levothyroxine in pregnancy from January 1, 2019 to May 11, 2020.

Micromedex,[3] ReproTox,[8] TERIS[9] and Shepard's[10] are all in agreement that levothyroxine does not cross the placenta and the fetal risk is minimal. There are risks to the mother and fetus if hypothyroidism is untreated in pregnancy. Maternal hypothyroidism during pregnancy can result in higher rates of complications, including spontaneous abortion, gestational hypertension, preeclampsia, stillbirth, and premature delivery. Untreated maternal hypothyroidism may have an adverse effect on fetal neurocognitive development. Adequate replacement in hypothyroid women is recommended to optimize pregnancy outcome. Micromedex[7] states "there have been no reports, including postmarketing studies, of major birth defects or miscarriages with the use of levothyroxine in pregnant women." ReproTox[8] states levothyroxine has not been clearly associated with an increased risk of congenital anomalies. Shepard's[10] states that "Heinonen et al.[11] found no increase in defects among 537 infants whose mothers used thyroid extract in the first 4 months. Wikner et al.[12] examined records from 10,055 pregnancies in which thyroxine was prescribed and found a small increased in congenital defects (OR 1.4, CI 1.05-1.26) but there was also an increase in pregnancy complications."

[8] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 3/12/2020.
[9] Teris database, Truven Health Analytics, Micromedex Solutions. Accessed 3/12/2020.
[10] 2020 Shepard's: A Catalog of Teratogenic Agent. Accessed 3/12/2020.
[11] Heinonen, O.P.; Slone, D. and Shapiro, S.: Birth Defects and Drugs in Pregnancy. Littleton, Mass.: John Wright-PSG, 1977, pp 397-398, 443.
[12] Wikner, B.N.; Sparre, L.S.; Stiller, C-O.; Kallen, B. and Asker, C.: Maternal use of thyroid hormones in pregnancy and neonatal outcome. Acta Obstetricia et Gynecologica 87:617-627, 2008.

Reviewer comment:
Overall published studies did not show an increase in the rate of miscarriage, malformations or adverse maternal or fetal outcomes.[13,14,15,16,17,18 19]

There are two studies from the National Birth Defect Registry data that suggest an increased risk of hydrocephalus associated with levothyroxine use in pregnancy; however, these studies were limited by the fact that they are registry based and unable to account for patient compliance. Because TSH levels were not measured, it was unclear if thyroid hormone replacement was optimized. This reviewer also noted that autoimmune antibodies were also not measured and their effects on pregnancy outcomes were unaccounted for.

Because hypothyroidism is associated with adverse pregnancy outcomes, such as spontaneous abortion, low birth weight, preterm delivery, gestational hypertension, preeclampsia, placental abruption, fetal loss, postpartum hemorrhage, and impaired neuropsychologic development of the offspring, levothyroxine replacement is necessary in pregnancy.

Glycerol

Glycerol is a polyol molecule that belongs to the alcohol family in organic chemistry. Glycerin is a commercial term when there is more than 95% glycerol in a product. In this review, the names will be used interchangeably as the same.

Glycerol is a precursor for synthesis of triacylglycerols and of phospholipids in the liver and adipose tissue. When the body uses stored fat as a source of energy, glycerol and fatty acids are released into the bloodstream. Glycerol is used as a food additive and in medical, pharmaceutical and personal care preparations. It is listed under Generally Recognized as Safe (GRAS) by the FDA. The Select Committee on GRAS Substances (SCOGS) concluded there is no evidence in the available information on glycerin that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future. It is also accepted as food additive by European Food Safety Authority (EFSA). The maximum daily exposure for glycerin listed under FDA Inactive Ingredient Database[20], which comprised of inactive ingredients of the approved drugs, is 31,536mg.

---

[13] Heinonen OP et al: Birth Defects and Drugs in Pregnancy. Littleton: Publishing Sciences Group. 1977: 388-400.
[14] Schurmann L, Hansen AV, Garne E. Pregnancy outcomes after fetal exposure to antithyroid medications or levothyroxine. Early Hum Dev. 2016 Jul 11; 101:73-77.
[15] Turunen S, et al. Pregnancy and perinatal outcome among hypothyroid mothers: A population-based cohort study. Thyroid 2019 29;1: 135-141.
[16] Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H 2006 Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 91:2587–2591
[17] Hallengren B, et al. Pregnant Women on Thyroxine Substitution Are Often Dysregulated in Early Pregnancy. Thyroid 2009 Apr;19(4):391-4. doi: 10.1089/thy.2008.0206.
[18] Taylor P, et al. TSH Levels and Risk of Miscarriage in Women on Long-Term Levothyroxine: A Community-Based Study. The Journal of Clinical Endocrinology & Metabolism. 2014; 99 (10): 3895–3902.
[19] Maraka S, et al. Effects of Levothyroxine Therapy on Pregnancy Outcomes in Women With Subclinical Hypothyroidism. Thyroid 2016;26(7):980-6.
[20] FDA Inactive Ingredient Search for Approved Drug Products (https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm?event=BasicSearch.page) Accessed 8/12/2020.

DPMH conducted a published literature review using Embase and Pubmed on the use of glycerin in pregnancy, two relevant articles were identified.

- An evaluation of glycerol as a food additive by the European Food Safety Authority states that there is no need for a numerical acceptable daily intake for glycerol (E422). There is no safety concern for glycerin as a food additive according to Annex II and III for the general population at the refined exposure assessment for the reported uses of glycerol as food additive.[21]
- A case report of a 24-year-old woman at 22-weeks gestation was treated with 6 weeks of meropenem and cefotaxime for a brain abscess. Glycerin (20g/day) was given to reduce intracranial pressure. She responded well to the therapy. At term, she delivered a normal female infant weight 2890g.[22]

Reviewer comment:
Glycerol is listed as GRAS, and FDA has not issued a recommended daily limit on consumption. EFSA also does not issue a recommended daily limit and felt there is no need to have a numerical acceptable daily limit. In the EFSA report, the highest exposure of glycerol was in a non-brand loyal consumer scenario with estimated dose of 460mg/kg body weight per day in children. By calculation, if the child weight >25kg, then he or she would have consumed more than (b) (4) *of glycerol per day. This is without adding additional glycerol consumption from animal and vegetable fat. Therefore, glycerol can be consumed from food at a level well above the* (b) (4) *that is presents in the maximum daily dose in levothyroxine oral solution.*

Micromedex[23] states that glycerin can be used orally, intravenously and as rectal suppository. Oral glycerin at 25-50g/kg or 0.5-1 g/kg intravenously has been used in treatment of cerebral edema, with subsequent doses of 0.25 to 0.5 g/kg orally every 4 to 6 hours. To reduce intraocular pressure, the recommended dose is 1 to 1.5 grams/kilogram orally as a 50% to 75% solution. The maximum daily use of glycerin administered is 120g per day.[24]
Glycerin previously had a Pregnancy Category C recommendation.

> "Glycerin has not been shown to have any adverse effect on the fetus (teratogenic or embryocidal) in animals. There have been no epidemiological studies or case reports concerning the use of glycerin in pregnant women. Use of glycerin as a hyperosmotic agent is not recommended during pregnancy due to concern that intravascular influx of fluid will lead to escape of intravascular fluid into the lungs and brain."

Reprotox[25] states that glycerin is present naturally in the body and is transferred across the placenta in small amounts.

[21] Mortensen A,e t al. Re-evaluation of glycerol (E 422) as a food additive. EFSA Journal 2017
[22] Yoshida M, Matsuda H, Furuya K. Successful prognosis of brain abscess during pregnancy. J Reprod Infertil 2013; 14:152-5
[23] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 4/15/2020.
[24] Gilman AG, 1990. Glycerol. Goodman and Gilman's The pharmacological basis of therapeutics. 8th Edition. Pergamon Press, New York, 715 pp.
[25] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 4/15/2020.

TERIS[26] states that glycerin is an organic alcohol that is used as a laxative, lubricant, and emollient and to reduce intraocular and intracranial pressure. Glycerin is also used as a cryoprotectant for freezing gametes and embryos for assisted reproductive technologies.

UpToDate[27] states that glycerin suppositories (5.4 g/dose fleet enema) are generally considered safe to use during pregnancy.[28,29]

Reviewer comment:
Published animal studies have not shown glycerol to be teratogenic, mutagenic or carcinogenic. Glycerin is considered by FDA to be 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. Therefore, the amount of glycerol in levothyroxine sodium oral solution is not expected to result in risks when used during pregnancy.

According to Micromedex, glycerol can be given orally at 25-50g as a hyperosmotic agent for cerebral edema, which is at a significantly greater dose than the maximum daily dose given with the levothyroxine sodium oral solution.

Overall, the applicant provided an adequate review of published literature regarding levothyroxine and glycerol use in pregnancy. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION
Nonclinical Experience
Animal studies have not been conducted with levothyroxine. There are no nonclinical pharmacology or toxicology studies provided with the submission.

Review of Clinical Trials
There were no lactating women present in the clinical trials.

Review of Literature
Applicant's Review of Literature
The applicant conducted an online search of published literature on PubMed and google regarding the use of levothyroxine during lactation as well as the use of glycerol during lactation. For full account of applicant's submission of review of literature in lactation, see applicant's submission on April 30, 2020, Module 1.11, under "Response to Maternal Health Information Request" (sequence number 005). The applicant found one relevant publication regarding thyroid hormone use and lactation, but none on glycerol.

- The 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum recommends

[26] TERIS. Accessed 4/15/2020.
[27] UpToDate Glycerin suppository. Access 3/24/2020
[28] Cullen G and O'Donoghue D, "Constipation and Pregnancy," Best Pract Res Clin Gastroenterol, 2007, 21(5):807-18
[29] Wald A, "Constipation, Diarrhea, and Symptomatic Hemorrhoids During Pregnancy," Gastroenterol Clin North Am, 2003, 32(1):309-22.

treatment of overt and subclinical hypothyroidism during lactation due to adverse impact of hypothyroidism on milk production and let down (weak recommendation, low-quality evidence).[30]

The applicant concluded:

> "[There are no] additional risks [identified] either for the mother or the breastfed baby, and overall supports a good benefit/risk ratio of the use of levothyroxine for the treatment of hypothyroidism during lactation. The applicant considers that these data support the proposed labelling information in section 8.2 Pregnancy, which is indeed the information included in the RLD (Synthroid®) label."

DPMH's Review of Literature

Levothyroxine

In 2019 DPMH review of levothyroxine by Christos Mastroyannis, MD,[6] DPMH noted:

> "Levothyroxine is present in breast milk in small amounts following maternal administration of oral levothyroxine. No adverse effects on the breastfed infant have been reported. All of the references cited agree that levothyroxine is compatible with breastfeeding."

DPMH conducted an updated published literature review, since 2019, in PubMed and Embase using the search terms "levothyroxine" AND "lactation" and "levothyroxine" AND "breastfeeding"; no additional articles were found.

The literature on the level of thyroxine naturally present in breastmilk is controversial. The amount of thyroxine present in milk is highly variable depending on the collection method used. Micromedex,[31] Lactmed,[32] Brigg's,[33] and Hale[34] all agree that human milk normally contains small quantities of thyroxine. The levels detected are too low to protect a hypothyroid infant completely from the effects of the disease. The levels are also too low to interfere with neonatal thyroid screening programs. There are no controlled studies regarding levothyroxine exposure

[30] Alexander, EK, Pearce, EN, Brent, GA, Brown, RS, Chen, H, Dosiou, C, Grobman, WA, Laurberg, P, Lazarus, JH, Mandel, SJ, Peeters, RP and Sullivan, S (2017). "2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum." Thyroid 27(3): 315-389.

[31] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 3/12/2020.

[32] http;//toxnet nlm nih.gov/newtoxnet/lactmed htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The lactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Access 4/15/20.

[33]Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 4/15/20

[34] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.

during lactation and milk production. Several studies[35,36,37,38] suggest maternal hypothyroidism can adversely affect milk production.[39] There is also a case report of a 4-month-old who is exclusively breastfed was diagnosed with failure to thrive. Shortly after, her mother was newly diagnosed with Hashimoto thyroiditis. Her milk supply improved after thyroxine replacement.[36] According to Micromedex[30] and Lactmed,[31] "replacing deficient thyroid levels should improve milk production caused by hypothyroidism." The American Academy of Pediatrics and World Health Organization both state that thyroxine is compatible with breastfeeding. Micromedex[31] gives the Lactation Rating "Infant risk is minimal." Hale[34] lists levothyroxine as "L1-Limited Data-Compatible."

Reviewer comment:
This reviewer did not find any reported cases of adverse effects from levothyroxine replacement in breastfeeding infants and agrees that thyroxine is present in minimal amounts in milk, naturally. [40,41,42,43,44]

Glycerol

DPMH conducted a literature search in PubMed and Embase on the use of glycerol during lactation; no relevant articles were identified.

Micromedex[45] gives glycerol the Lactation Rating: "Infant risk cannot be ruled out." In addition, Micromedex states:

> "No reports describing the use of glycerin during human lactation are available and the effects on the nursing infant from exposure to the drug in milk are unknown. It is not known if glycerin affects the quantity and composition of breastmilk. Until more data is available, use caution when considering glycerin in lactating women."

[35] Buckshee K, Kriplani A, Kapil A, Bhargava VL, Takkar D. Hypothyroidism complicating pregnancy. Aust N Z J Obstet Gynaecol 1992; 32:240–242.
[36] Stein MT, Kessler DB, Hubbard E Failure to thrive in a four-month-old nursing infant. J Dev Behav Pediatr 2004;25: S69–S73.
[37] Hapon MB, Varas SM, Gime´nez MS, Jahn GA 2007 Reduction of mammary and liver lipogenesis and alter-ation of milk composition during lactation in rats by hy-pothyroidism. Thyroid 17:11–18.
[38] Thrift TA, Bernal A, Lewis AW, Neuendorff DA, Willard CC, Randel RD. Effects of induced hypothyroidism on weight gains, lactation, and reproductive performance of primiparous Brahman cows. J Anim Sci 1999; 77:1844–1850.
[39] Alexander EK, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017;27(3): 315-389.
[40] Sack J, Amado O, Lunenfeld B. Thyroxine concentration in human milk. J Clin Endocrinol Metab 1977; 45:171-3
[41] Mizuta H, Amino N, Ichihara K, Harada T, Nose O, Tanizawa O, Miyai K. Thyroid hormones in human milk and their influence on thyroid function of breast-fed babies. Pediatr Res 1983; 17:468-71.
[42] Varma SK, Collins M, Row A, Haller WS, Varma K. Thyroxine, triiodothyronine, and reverse triiodothyronine concentrations in human milk. J Pediatr 1978; 93:803-6.
[43] Moller B, Bjorkhem I, Falk O, Lantto O, Larsson A. Identification of thyroxine in human breast milk by gas chromatography-mass spectrometry. J Clin Endocrinol Metab 1983; 56:30-4.
[44] Jansson L, Ivarsson S, Larsson I, Ekman R. Tri-iodothyronine and thyroxine in human milk. Acta Paediatr Scand 1983; 72:703-5.
[45] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 3/12/2020.

Brigg's[46] and Hale[47] both state that as a laxative, glycerol is probably compatible. There are no data available in lactation.

Reviewer comment:
Overall, the applicant provided an adequate review of published literature regarding levothyroxine and glycerol use in lactating women. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

There have been no animal studies conducted to evaluate the effects of levothyroxine on fertility. There are no nonclinical pharmacology or toxicology studies provided with the submission.

Review of Clinical Trials

There were no cases of infertility present in the clinical trials.

Review of Literature

Applicant's Review of Literature

The applicant conducted an online search of published literature in PubMed regarding the use of levothyroxine and fertility. In addition, the applicant also conducted a search in PubMed and Google regarding the use of glycerol and fertility. For full account of applicant's submission of review of literature in female and males of reproductive potential, see applicant's submission on April 30, 2020, Module 1.11, under "Response to Maternal Health Information Request" (sequence number 005). The applicant found several relevant publications regarding thyroid hormone use but none regarding glycerol use. One publication of interest is listed below:

- A study of 15 euthyroid men with idiopathic infertility compared sperm parameters before and after treatment with thyroid hormone. Thyroid hormone increased the percentage of spermatozoa with high mitochondrial membrane potential (MMP), decreased the percentage of spermatozoa with low MMP and increased sperm motility. Therefore, thyroid hormone reduced sperm necrosis and lipid peroxidation ameliorating chromatin compactness.[48]

The applicant concluded:

> "Thyroid autoimmunity (TAI) and/or thyroid dysfunction have independently been associated with adverse fertility and pregnancy outcomes, in the case of spontaneous conception or after assisted reproductive technology (ART). Overt thyroid dysfunction often leads to menstrual disturbances, fertility problems and pregnancy complications and should therefore be treated accordingly... These studies do not [identify any drug-related] negative effect on female and male fertility... Subsection 8.3 should be omitted."

[46]Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 10/17/2019

[47] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.

[48] Condorelly RA, et al. Thyroid Hormones and Spermatozoa: In Vitro Effects on Sperm Mitochondria, Viability and DNA Integrity. J Clin Med 2019 May 27;8(5)756. doi: 10.3390/jcm8050756.

DPMH's review of literature

Levothyroxine

Both reviewers of the 2016[49] and 2019[7] DPMH reviews of levothyroxine concluded "there is no evidence in the literature to suggest that levothyroxine adversely affects male or female fertility."

DPMH conducted an updated published literature review, since 2019, using Embase, Pubmed, Micromedex,[50] ReproTox,[51] and TERIS.[52] Search terms used were "levothyroxine AND reproduction," "levothyroxine AND infertility," and "levothyroxine AND contraception."

- There is no evidence to show levothyroxine adversely affects fertility.

ReproTox[51] states there was a Japanese study that reported on the use of thyroxine for patients with subclinical hypothyroidism and infertility.[53] Among 69 women, 58 (84.1%) conceived during treatment with thyroxine, although 17 of these patients (29.3%) miscarried. No information was provided on the health of the offspring from the successful pregnancies.

Reviewer comment:
This reviewer agrees with the prior DPMH reviewer's conclusion that there is no evidence to show levothyroxine adversely affects fertility. Hypothyroidism may contribute to infertility, and levothyroxine treatment restores normal function, and therefore, is utilized in treatment of infertility patients with subclinical hypothyroidism.

Guidance Labeling for combined Hormonal Contraceptives Draft published December 2017 states:

> "Concomitant use of [combined hormonal contraceptive] with thyroid hormone replacement therapy or corticosteroid replacement therapy may increase systemic exposure of thyroid-bind and cortisol-binding globin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased."

Proposed product label, subsection 7.1 Drugs Known to Affect Thyroid Hormone Pharmacokinetics lists oral contraceptives under Table 2. Drugs that may decreased T4 absorption.

> Potential impact: Concurrent use may reduce the efficacy of TRADENAME by binding and delaying or preventing absorption, potentially resulting in hypothyroidism.
> Effect: Estrogen-containing oral contraceptives and oral estrogen may interact with levothyroxine by increased serum thyroxine-binding globulin (TBG) concentration.

---

[49] DPMH review of NDA 206977 by Jacqueline Spaulding, MD, on November 11, 2011, DARRTS Reference ID 206977

[50] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 3/12/2020

[51] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 3/12/2020.

[52] Teris database, Truven Health Analytics, Micromedex Solutions, Accessed 3/12/2020

[53] Yoshioka W, Amino N, Ide A, Kang S, Kudo T, Nishihara E, Ito M, Nakamura H, Miyauchi A. 2015. Thyroxine treatment may be useful for subclinical hypothyroidism in patients with female infertility. Endocr J 62(1): 87-92. https://www.jstage.jst.go.jp/article/endocrj/62/1/62_EJ14-0300/_pdf

Reviewer comment:
Although co-administration with oral birth control pills may transiently interfere with the amount of free T4 that is bioavailable, the co-administration of both medications does not affect the efficacy of birth control pills. This is already address under subsection 7.1 of the proposed product label. Therefore, no addition to subsection 8.3 is warranted here.

Glycerol

DPMH conducted a literature search in PubMed and Embase on the effect of glycerol on male or female fertility, one article was identified.

- A review article discussed recent rise in metabolic disorders (which lead to high extracellular glycerol concentration) and decline in semen quality. The article noted that experiments demonstrated that when glycerol is present in high concentrations in the testis via intratesticular administration, it causes blood-testis barrier disruption, impairing tubular fluid homeostasis and promoting the apoptosis of germ line cells. This phenomenon causes temporary spermatogenesis arrest, but if persists for some time may cause permanent oligospermia or even azoospermia.[54]

ReproTox[55] states that glycerin has been used as a permeating protectant in the cryopreservation of human spermatozoa and embryo. Glycerin-containing vaginal lubricants might impair sperm motility. When given orally to male rats at a dose level of 100 mg/kg, glycerin had no effect on fertility.

Reviewer comment:
There are no clinical data on the oral administration of glycerol on fertility in humans. Although this review article noted a possible mechanism of glycerol and male fertility, its effect was noted after intratesticular administration of glycerol solutions, which is different than the route of administration in this product.

Overall, the applicant provided an adequate review of published literature regarding levothyroxine and glycerol use in males and females of reproductive potential. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

The clinical data in pregnant women treated with oral levothyroxine to maintain a euthyroid state have not reported increased rates of major birth defects, miscarriages, or adverse maternal or fetal outcomes. Because hypothyroidism can lead to adverse pregnancy and neonatal outcomes, including spontaneous abortion, gestational hypertension, preeclampsia, stillbirth, premature delivery, and adverse effect on fetal neurocognitive development, hypothyroidism needs to be treated during pregnancy.

[54] Crisostomo L, et al. Glycerol and testicular activity: the good, the bad and the ugly. Molecular Human Reproduction 2017;23(11): 725–737. doi:10.1093/molehr/gax049
[55] ReproTox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 4/15/2020.

Published literature on oral glycerin use in pregnancy is limited to one case report. 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.

Levothyroxine is used in females of reproductive potential and in pregnancy. There is no safety concern for levothyroxine or glycerol at the current time with use in pregnancy at the recommended dose. DPMH does not recommend any postmarking pregnancy study.

Lactation

Thyroxine is produced naturally and is present in minimal amounts in human milk. There are no reported cases of adverse effect from levothyroxine replacement in mothers of breastfeeding infants. All the references agree that levothyroxine is compatible with breastfeeding. Hypothyroidism decreases milk production in some women. There is a case report of levothyroxine supplementation in a hypothyroid mother that improved milk supply. It is reasonable to expect a woman with diminished milk production secondary to hypothyroidism would have improvement in milk production with thyroxine hormone replacement. This is present in the approved labeling of RDL, Synthroid. DPMH agrees with the approach of current Synthroid labeling.

There are no available data on the presence of glycerin in human milk. There are no reports of adverse effect on the breastfed infant. The effect of glycerin on milk production is unknown. Glycerin is GRAS and the proposed daily maximum dose is within the accepted range in food and beverages by ESFU.

Levothyroxine has been used in females of reproductive potential and in lactating women for several decades. There is no safety concern for levothyroxine or glycerol at the current time with use in lactation. DPMH does not recommend any postmarking lactation study.

Females and Males of Reproductive Potential

There is no evidence in the literature to suggest that levothyroxine adversely affects male or female fertility. There is also no evidence in the literature to suggest that oral ingestion of glycerin has any impact on fertility in females and males of reproductive potential. Glycerin is not genotoxic or carcinogenic. It has no impact on fertility in rats.

Although estrogen containing birth controls may affect the amount of free T4 available by increase serum concentration of TBG transiently, there are no effects on efficacy of hormonal birth control. There is no reported drug to drug interaction (DDI) of glycerol and hormonal contraception. Since this DDI has been already address under subsection 7.1 of the proposed labeling, no additional recommendation is needed under subsection 8.3. DPMH recommends omitting subsection 8.3.

LABELING RECOMMENDATIONS
DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH recommendations are below and reflect the discussions with Division of General Endocrinology. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: May require the use of higher doses of TRADENAME during pregnancy. (2.3, 8.1)

FULL PRESCRIBING INFORMATION
2 DOSAGE AND ADMINISTRATION
2.3 Dosing in Specific Patient Populations
Pregnancy
Pre-existing Hypothyroidism: TRADENAME dose requirements may increase during pregnancy. Measure serum TSH and free-T4 as soon as pregnancy is confirmed and, at minimum, during each trimester of pregnancy. In patients with primary hypothyroidism, maintain serum TSH in the trimester-specific reference range. For patients with serum TSH above the normal trimester- specific range, increase the dose of TRADENAME by 12.5 to 25 mcg/day and measure TSH every 4 weeks until a stable TRADENAME dose is reached and serum TSH is within the normal trimester-specific range. Reduce TRADENAME dosage to pre-pregnancy levels immediately after delivery and measure serum TSH levels 4 to 8 weeks postpartum to ensure TRADENAME dose is appropriate.

New Onset Hypothyroidism: Normalize thyroid function as rapidly as possible. (b) (4) (b) (4) (b) (4) Evaluate serum TSH every 4 weeks and adjust TRADENAME dosage until a serum TSH is within the normal trimester specific range *[see Use in Specific Populations (8.1)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Prolonged experience with levothyroxine use in pregnant women, including data from postmarketing studies, to maintain a euthyroid state have not reported increased rates of major birth defects, miscarriages, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated hypothyroidism in pregnancy. Since thyroid-stimulating hormone (TSH) levels may increase during pregnancy, TSH should be monitored and TRADENAME dosage adjusted during pregnancy *(see Clinical Considerations).* There are no animal studies conducted with levothyroxine during pregnancy. Levothyroxine should not be

discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Maternal hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, pre-eclampsia, stillbirth, gestational hypertension, and premature delivery. Untreated maternal hypothyroidism may have an adverse effect on fetal neurocognitive development.

Dose Adjustments During Pregnancy and the Postpartum Period

Pregnancy may increase TRADENAME requirements. Serum TSH levels should be monitored and the TRADENAME dosage adjusted during pregnancy. Since postpartum TSH levels are similar to preconception values, the TRADENAME dosage should return to the pre-pregnancy dose immediately after delivery *[see Dosage and Administration (2.3)]*.

8.2 Lactation

Risk Summary

Published studies report that levothyroxine is present in human milk. No adverse effects on the breastfed infant have been reported and there is no information on the effects of levothyroxine on milk production. Adequate levothyroxine treatment during lactation may normalize milk production in hypothyroid lactating mothers with low milk supply. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

APPENDIX A. Summary of Studies in previous DPMH Reviews of Levothyoxine use in Pregnancy[56] (Reviewer's Table)

Publication; author/date/Country	Type of study	Population/control/n/disease	N	Exposure time	Outcomes	Comments
Nergo et al.[57] (2006) Italy	Prospective controlled	57 Thyroid peroxidase (TPO Antibody (Ab)+ euthyroid women were treated with thyroid hormone from 2002-2004 vs 58 was not treated, compared with 869 TPO- women as control.	984 total, 57 treated	All	-Those treated have similar miscarriage rate as control (3.5 and 2.4% respectively). Those not treated with TPO Ab + had a miscarriage rate of 12.8% (RR=4.95; 95% CI 2.59-9.48). -Those treated have similar premature deliveries as control (7% and 8.2% respectively). Those not treated with TPO Ab+ had a premature delivery rate of 22.4% (RR 12.18; 95% CI 7.98-18.7).	-Pros: prospective and controlled -Cons: small group, not randomized
Wilkner BN, et al.[58] (2008) Sweden	Population-based cohort	Pregnant women who reported use of thyroid hormones vs those who did not in Swedish Health Registers and Swedish Medical Birth register	9866 women, 10055 infants (5006 received script later in pregnancy; 19% had no reported use in early pregnancy)	varies, levothyroxine	-Women using thyroxine had an increased rate of pre-eclampsia, diabetes (pre-existing or gestational), cesarean sections and inductions of labor compared to women in the reference population. The risk for preterm birth was marginally increased (OR 1.13, 95% CI 1.03-1.25). - A small but statistically significant risk for congenital malformations (OR =1.14, 95% CI 1.05-1.26) was found. -Neonatal thyroid disease was found in eight infants (seven with thyrotoxicosis and one unspecified)	-Cons: in term of malformations, the data were not focused on 1st trimester -disease severity not adjusted; how well disease was controlled is unknown. -registry study
Brown ML, et al.[59] (2009) USA	population-based, case-control study	14,067 infant cases (316 with thyroid disease) with birth defect in the National Birth Defects Prevention Study (1997-2004). vs 5875 controls (111 with thyroid	14067 with birth defect (316 with thyroid disease)	3-month prior pregnancy and pregnancy : thyroid	There were statistically significant associations between maternal thyroid disease and left ventricular outflow tract obstruction heart defects (1.5; 95% CI, 1.0-2.3), hydrocephaly (2.9; 95% CI, 1.6-5.2), hypospadias (1.6; 95% CI, 1.0-2.5),	-Pros: Preexisting maternal diabetes was excluded from this study (but not many other studies) -Cons: retrospective at risk for recall bias; lack of

[56] DPMH review of NDA 206977 on November 11, 2011, DARRTS Reference ID 206977

[57] Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H 2006 Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 91:2587–2591

[58] Wikner BN, Sparre LS, Stiller CO, et al: Maternal use of thyroid hormones in pregnancy and neonatal outcome. Acta Obstet Gyneocol Scand 2008; 87(6):617-27.

[59] Brown Ml, et al. Maternal thyroid disease, thyroid medication use, and selected birth defects in the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol 2009; 85(7):621-8.

		disease) randomly select from hospital records		hormone and anti-thyroid drug (ATD)	and isolated anorectal atresia (2.4; 95% CI, 1.2-4.6). Estimates for the association between periconceptional use of thyroxine and specific types of birth defects were similar to estimates for any thyroid disease.	thyroid function data; drug effect cannot be separated from disease (such as effect of autoantibodies)
Hallengren B, et al.[60] (2009) Sweden	prospective opened label	63 pregnant women (1997-2002) on thyroid hormone for hypothyroidism, those with serum TSH within reference range were compared to those outside the range	63	All (83% were in 1st trimester when started)	Fetal loss rate was 6% (2 out of 32) in women with TSH in the normal range women compared to 29% (9 out of 31) in the women with TSH outside normal range (12 had TSH < 0.4 mIU/L and 19 had TSH > 4 mIU/L) ($p<0.05$).	-Pros: controlled, prospective; TSH was measured -Cons: small study
Taylor P, et al.[61] (2014) UK	population-based cohort	1013 women on thyroid hormone from 55,501 women from UK Clinical Practice Research database (2001-2009)	987	6 months prior to conception and pregnancy	Women with TSH > 2.5 mU/L in the 1st trimester had an increased risk of miscarriage compared with women with TSH between 0.2-2.5 mIU/L. -TSH 2.51-4.5 mU/L [OR 1.09, (95% CI 0.61, 1.93)] -TSH 4.51-10 mU/L [OR 1.81, (95% CI 1.03, 3.14)] -TSH > 10 mU/L [OR 3.95, (95% CI 1.87, 8.37)]	-Pros: controlled, prospective; TSH was measured; adjusted for age, year of pregnancy, diabetes and social class.
Maraka S, et al.[62] (2016) USA	Observational retrospective cohort	Women received thyroid hormone (n=82) with subclinical hypothyroidism (SCH) in the 1st trimester vs those did not (n=284) from 2011-2013	366	Anytime during pregnancy	Those who received thyroid hormone had fewer pregnancy losses (6.1% vs 8.8% respectively but not statistically significant, $p=0.12$), fewer low birth weight children (1.3% vs 10%; $p<0.001$), and no neonates with 5- minute Apgar score <7 (0% vs 7%; $p<0.001$)	-Cons- not randomized; retrospective; no specified starting time for thyroid hormone
Schurmann L, et al.[63] (2016) Denmark	population-based cohort	Cohort of all pregnancies from 12 weeks gestation recorded in Danish registries from 1995-2010 comparing those with exposure to thyroid hormone or ATD (n=8318) and those without (n=969,303). A subpopulation was linked to the Danish	6475 (hypothyroid) 1843 (hyperthyroid)	91 days before and 1st trimester; Thyroid hormone and ATD	-There was no difference in proportion of live births compared to non-exposed pregnancies -Prevalence of congenital anomalies was the same for exposed and non-exposed pregnancies. -Treatment for hypothyroidism had no significant impact gestational age, birth weight, length and infant mortality	-Pros: epilepsy and diabetes excluded -Cons: data based on registry, script fill but may or may not be taking the medication, whether the medication resulted in euthyroid state is unknown.

[60] Hallengren B, et al. Pregnant Women on Thyroxine Substitution Are Often Dysregulated in Early Pregnancy. Thyroid 2009 Apr;19(4):391-4. doi: 10.1089/thy.2008.0206.

[61] Taylor P, et al. TSH Levels and Risk of Miscarriage in Women on Long-Term Levothyroxine: A Community-Based Study. The Journal of Clinical Endocrinology & Metabolism. 2014; 99 (10): 3895–3902. https://doi.org/10.1210/jc.2014-1954

[62] Maraka S, et al. Effects of Levothyroxine Therapy on Pregnancy Outcomes in Women With Subclinical Hypothyroidism. Thyroid 2016;26(7):980-6. doi: 10.1089/thy.2016.0014.

[63] Schurmann L, Hansen AV, Garne E. Pregnancy outcomes after fetal exposure to antithyroid medications or levothyroxine. Early Hum Dev. 2016 Jul 11;101:73-77. doi:10.1016/j.earlhumdev.2016.06.006. [Epub ahead of print] PubMed PMID:27416058.

		EUROCAT congenital anomaly register.				
Howley MM, et al.[64] (2017) USA	population-based, case-control study	31,409 infant cases (738 on thyroid hormone, 34 on ATD) with birth defect in the National Birth Defects Prevention Study (1997-2011). vs 11,536 controls (237 on thyroid hormone, 10 on ATD)	31,409 cases, 738 on thyroid hormone	month before conception through 1st trimester; thyroid hormone and ATD	Thyroid hormone was associated with: -anencephaly (OR = 1.68; 95% CI, 1.03-2.73), -holoprosencephaly (OR = 2.48; 95% CI, 1.13-5.44), -hydrocephaly (1.77; 95% CI, 1.07-2.95) -small intestinal atresia (OR = 1.81; 95% CI, 1.04-3.15).	-Cons: retrospective at risk for recall bias; lack of thyroid function data; drug effect cannot be separated from disease (such as effect of autoantibodies)

APPENDIX B. DPMH updated literature on the use of levothyroxine in Pregnancy (reviewer's table)

Publication; author/date/Country	Type of study	Population/control/n/disease	N	Exposure time	Outcomes	Comments
Sun X, et al.[65] (2020) China	Meta-analysis	Review of pregnancy outcomes in 4 randomized controlled trials (RCTs) and 2 retrospective studies of thyroid hormone use in euthyroid women with thyroid autoimmunity (TAI)	2249 pregnant women (6 studies)	Before and during pregnancy	No benefit (in terms of spontaneous abortions, preterm birth rate, live birth rate) in euthyroid women with TAI treated in pregnancy over all, or prior to pregnancy. Women who initiated LT4 treatment in early pregnancy had a significantly lower preterm birth rate (RR 0.54, 95% CI: 0.31-0.92, I2 = 0%) than those who received no treatment or placebo.	L-mixed quality and type of data with different reference ranges for thyroid function; definition of TAI is slightly different between the studies (all included TPO ab but not all included antithyroglobulin antibody (Tgab)) publication bias not assessed
Leduc-Robert G, et al.[66] (2020) Canada	Retrospective cohort study	Evaluate if initiating levothyroxine treatment based on thyroid-stimulating hormone (TSH) (0.1-<2.5 mIU/l; 2.5-≤4 mIU/l; 4- ≤10	1064	Before and during pregnancy	Treatment of hypothyroidism in pregnancy should be initiated based on a TSH >4 mIU/l. Treatment initiation based on thyroid autoimmunity or a TSH >2.5 mIU/l may result in overtreatment.	S- large size L-pregnancy loss was assessed at 10 weeks only; lower TPOAb used here than some studies (35 IU/ml vs 100 IU/ml); underlying

[64] Howley MM, Fisher SC, Vn Zutphen AR, Waller DK, Carmichael SL, Browne ML, and the National Birth Defects Prevention Study. Thyroid medication use and birth defects in the National Birth Defects Preventions Study. Birth Defects Res 2017;109:1471-1481.
[65] Sun, X, et al. A Meta-Analysis of Pregnancy Outcomes with Levothyroxine Treatment in Euthyroid Women With Thyroid Autoimmunity. J Clin Endocrinol Metab 2020 Apr 1; 105(4).
[66] Leduc-Robert, et al. Prevalence of thyroid autoimmunity and effect of levothyroxine treatment in a cohort of 1064 patients with recurrent pregnancy loss. Reprod Biomed Online. 202 Apr;40(4):582-592.

		mIU/L) or TAI improve pregnancy continuation rate in recurrent pregnancy loss (RPL) patients.				assumption that treatments of other concurrent factors contributing to RPL were effective; non-adherence was not corrected.
Dhillon-Smith, et al.[67] (2019) UK	RCT-double blinded	952 out of 19,585 euthyroid women (with miscarriage or undergoing fertility evaluation) tested in UK (2011-2016) have thyroid peroxidase antibodies (TPOs). 476 received 50 μg daily levothyroxine vs 476 received placebo.	952	Conception through to the end of pregnancy	540 became pregnant and 354 had a baby after 34 weeks. No difference in live birth rate after 34 weeks (37.4% treated vs 37.9% placebo).	S-RCT; large sample size; TSH was followed throughout pregnancy; compliance was measured L- variation of threshold out TPOAb at time of randomization across various trial sites; possible suboptimal treatment -live birth is defined as birth after 34 weeks; TgAb not considered;
Nazarpour S, et al.[68] (2019) Iran	Meta-analysis	-T4 treatment on pregnancy outcomes in subclinical hypothyroidism (SCH).	11,503 women 13cohort studies and RCT	variable	-Pregnant women with SCH treated with levothyroxine had lower chances of pregnancy loss (OR 0.78, 95% CI 0.66–0.94; I2 = 0%) and higher chances for live birth rates (OR 2.72, 95% CI 1.44–5.11; I2 = 25%) than the placebo group. -Compared to euthyroid women, SCH patients treated with levothyroxine had higher odds ratio for preterm labor (OR 1.82, 95% CI 1.14–2.91; I2 = 0%).	L-heterogenous studies including different reference for TPOab and some studies did not include testing for TPOab, variable levothyroxine dose.
Korevaar TIM, et al.[69] (2019) USA	Meta-analysis	- evaluation of thyroid function test abnormalities or thyroid autoimmunity as a risk factor for preterm birth	47,045 women, 19 prospective cohort studies	All	<u>Risk of preterm labor</u> - subclinical hypothyroidism vs euthyroid women, 6.1% vs 5%, OR 1.29 (95% CI, 1.01-1.64) -isolated hypothyroxinemia vs euthyroid women, 7.5% vs 5%, OR, 1.46 (95% CI, 1.12-1.90)	L-only 5 of 19 studies reported TgAb; causality cannot be determined from observational studies.

[67] Dhillon-Smith RK, et al. Levothyroxine to Increase Live Births in Euthyroid Women With Thyroid Antibodies Trying to Conceive: The TABLET RCT. Efficacy and Mechanism Evaluation 2019;6(11)

[68] Nazarpour S., Ramezani Tehrani F., Amiri M., Bidhendi Yarandi R., Azizi F. Levothyroxine treatment and pregnancy outcomes in women with subclinical hypothyroidism: a systematic review and meta-analysis. Archives of Gynecology and Obstetrics 2019 300:4 (805-819)

[69] Korevaar TIM, et al. The consortium on Thyroid and Pregnancy-Study Group on Preterm Labor. Association of Thyroid Function Test Abnormalities and Thyroid Autoimmunity with Preterm Birth: A Systematic Review and Meta-analysis. Journal of the American Medical Association 2019 322:7 (632-641)

					-thyroid peroxidase antibody positivity vs euthyroid women, 6/6% vs 5%, OR 1.33 (95% CI, 1.15-1.56).	
Akhtar MA, et al.[70] (2019) UK	Cochrane Database Review	- evaluate the efficacy and harms of levothyroxine replacement in subfertile women with SCH or euthyroid women with TAI undergoing assisted reproduction.	820 women 4 RCT	Prior to pregnancy and 1st trimester	We could draw no clear conclusions in this systematic review due to the very low to low quality of the evidence reported.	

[70] Akhtar M.A., Agrawal R., Brown J., Sajjad Y., Craciunas L.
Cochrane Database of Systematic Reviews 2019 2019:6 Article Number CD011009

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/

WENJIE SUN
09/01/2020 08:59:20 AM

MIRIAM C DINATALE
09/01/2020 09:07:50 AM

LYNNE P YAO
09/02/2020 01:48:48 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 23, 2020
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 214047
Product Name, Dosage Form, and Strength:	Thyquidity [a](levothyroxine sodium) oral solution, 100 mcg/5 mL (20 mcg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	EMP Levo
FDA Received Date:	January 31, 2020 and July 6, 2020
OSE RCM #:	2020-221 2020-222
DMEPA Safety Evaluator:	Melina Fanari, RPh
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

[a] Request for proposed proprietary name Thyquidity was submitted on June 4, 2020. The name is currently under review.

1 REASON FOR REVIEW

As part of the 505(b)(2) NDA approval for Thyquidity (levothyroxine sodium) oral solution, the Division of General Endocrinology (DGE) requested that we review the proposed Thyquidity Prescribing Information (PI), container label and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other (Human Factors Use Related Risk Analysis)	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 REVIEW SUMMARY AND DISCUSSION

In the January 31, 2020 NDA submission, EMP Levo proposed (b) (4) the levothyroxine sodium oral solution (b) (4) labeling. (b) (4) (b) (4) Upon preliminary review of the proposed product packaging configuration, DMEPA considered the design of the proposed (b) (4) confusing, error prone and likely to lead to wrong dose medication errors. On June 16, 2020, we sent an information request (IR) detailing the medication error risks associated with the proposed (b) (4) (b) (4) design and a request to address the identified risks and provide a mitigation plan.[b] In response to the IR, the Applicant amended the NDA on July 6, 2020 (b) (4)

[b]Galgay, L. Information Request for NDA 214047, levothyroxine oral solution. Silver Spring (MD): FDA, CDER, OND, (US); 2020 Jun 16

(b) (4) and provided revised labels and labeling to propose patients utilize a pharmacist provided oral syringe for dosing commensurate with their prescribed dose.

3.1 HUMAN FACTORS ASSESSMENT /USE RELATED RISK ANALYSIS (URRA)

The Applicant submitted a Use-Related Risk Analysis (URRA) and their justification that a human factors (HF) validation study is not necessary for Levothyroxine Sodium Oral Solution (b) (4) (b) (4). As stated above, see section 3.1, the Applicant is no longer planning on (b) (4) (b) (4), therefore, the submitted URRA and the HF information is no longer applicable to the proposed product. Our evaluation of the July 6, 2020 revised packaging configuration did not identify any new use-related risks for the proposed product. We acknowledge that the revised labels and labeling proposes utilizing an oral syringe which will be provided to the patient by a health care provider at the time of the product dispensing. Therefore, based on the submitted information and postmarket experience with similar products, we determined that the Applicant is not required to submit any additional human factors (HF) information to support their marketing application.

3.2 DISCUSSION

Thyquidity will be the first bulk volume levothyroxine oral solution to be introduced in the market place. It will be available in a 100 mL bottle with a concentration of 100 mcg/5 mL (20 mcg/mL). The initial NDA submission included a proposal to (b) (4) (b) (4). The review team considered the design of the proposed (b) (4) confusing, error prone and likely to lead to wrong dose medication errors. In addition, due to the wide range of dosing for levothyroxine, it is unlikely that a (b) (4) would be able to provide all labeled doses to patients. Based on our initial feedback related to this packaging configuration, the Applicant has amended their NDA (b) (4) and is now proposing revised product labeling recommending the use of a pharmacy provided oral syringe with standard numeric graduations (e.g. 0.1 mL, 0.25, or 0.5 mL) for dosing commensurate with the patients prescribed dose. The pharmacy-provided syringe would allow a pharmacist to provide a syringe with a volume specific to the patients prescribed dose. Based on the proposed product concentration (20 mcg/mL) and currently available oral syringes in the market place, a patient could be dosed in increments as low as 2 mcg (0.1 mL) providing for increased dosing accuracy and reducing the risk of wrong dose medication errors. We consider the Applicants proposal (b) (4) acceptable and less likely to lead to wrong dose medication errors. Further, the use (b) (4) is not necessary for the safe use of the product.

4 FINDINGS AND RECOMMENDATIONS

Table 2 below includes the identified medication error issues with the submitted container label and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Our evaluation of the proposed Prescribing Information did not identify any areas of vulnerability that may lead to medication errors.

Table 2. Identified Issues and Recommendations for EMP Levo (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
ALL Carton Labeling and Container Labels			
1.	NDC number is denoted by a placeholder.	Per 21 CFR 207.33	Revise the placeholder NDC with the numerical NDC number.
2.	Expiration date is missing (carton labeling) or undefined (container label).	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

Table 2. Identified Issues and Recommendations for EMP Levo (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The product identifier required under the drug supply chair security act (DSCSA) is missing.	DSCSA requires manufacturers and repackages, respectively, to affix or imprint a product identifier to each package and homogeneous case of a product intended to be introduced in a transaction in (to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf
4.	'Dispense and store in original container' statement is on side panel missing.	Per 21 CFR 201.100 (b)(7).	Consider relocating the 'Dispense and store in original container" statement on the principal display panel.
5.	Usual dosage statement requires revisions.	Per 21 CFR 201.55.	Revise the usual dosage statement to read as follows: "Recommended Dosage: See prescribing information."
Container Label			
1.	Date of first opening statement requires revisions.	Reduce risk for deteriorated drug medication errors.	We recommend "Discard after __/__/__" instead of (b) (4) (b) (4) since "Discard after" is an affirmative statement and has been shown to result in the desired action.

3 CONCLUSION

Our evaluation of the proposed Thyquidity Prescribing Information (PI), container label and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table for the Applicant. We ask that the Division convey Table 2 in its entirety to EMP Levo so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Thyquidity received on July 6, 2020 from EMP Levo, and the listed drug (LD).

Table 2. Relevant Product Information for Thyquidity and the Listed Drug		
Product Name	Thyquidity	Synthroid[c]
Initial Approval Date	N/A	2002
Active Ingredient	Levothyroxine sodium	Levothyroxine sodium
Indication	Adults and pediatric patients: -Hypothyroidism - As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism. -Pituitary Thyrotropin (Thyroid Stimulating Hormone, TSH) Suppression - As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.	Adults and pediatric patients: -Hypothyroidism - As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism. -Pituitary Thyrotropin (Thyroid Stimulating Hormone, TSH) Suppression - As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.
Route of Administration	Oral	Oral
Dosage Form	solution	tablet
Strength	100 mcg/5 mL (20 mcg/mL)	(b) (4) 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg
Dose and Frequency	Administer once daily, on an empty stomach, one-half to one hour before breakfast.	Administer once daily, on an empty stomach, one-half to one hour before breakfast.

[c] Synthroid [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 Apr 17 Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021402s024s028lbl.pdf.

	Average dose is 1.6 mcg/kg/day and adjust by 12.5 to 25 mcg every 4-6 weeks. Dosing is variable in specific patient populations and adequacy of therapy determined with periodic monitoring of TSH and/or T4 as well as clinical status.	Average dose is 1.6 mcg/kg/day and adjust by 12.5 to 25 mcg every 4-6 weeks. Dosing is variable in specific patient populations and adequacy of therapy determined with periodic monitoring of TSH and/or T4 as well as clinical status.
How Supplied	Clear, colorless to nearly colorless solution supplied in a 100 mL amber glass bottle.	Supplied in bottles of 90, 100, 1000 tablets and unit dose cartons of 100 tablets.
Storage	Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from light. Store and dispense in original bottle. Use within 8 weeks of opening the bottle.	Store at 25°C (77°F); excursions permitted to 15°-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light and moisture.

APPENDIX E. OTHER (HUMAN FACTORS USE RELATED RISK ANALYSIS)

The URRA report can be accessible in EDR via:
\\CDSESUB1\evsprod\NDA214047\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hypothyro-tsh-suppress\5354-other-stud-rep\urra

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Thyquidity labels and labeling submitted by EMP Levo.

- Container label received on July 6, 2020
- Carton labeling received on July 6, 2020
- Prescribing Information (Image not shown) received on July 6, 2020, available from \\CDSESUB1\evsprod\NDA214047\0012\m1\us\114-labeling\114a-draft-label

F.2 Label and Labeling Images

Container Labels

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling

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/

MELINA N FANARI
07/23/2020 04:58:33 PM

SEVAN H KOLEJIAN
07/23/2020 05:08:43 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/30/2020

TO: Division of Metabolism and Endcrinology Products
Office of Drug Evaluation

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 214047

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The clinical inspection was conducted in June 2019 and the analytical inspection was conducted in September 2019, which falls within the surveillance interval. The inspections were conducted under the following submissions: NON-RESPONSIVE .

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the rationale provided above, an inspection is not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	(b) (4)	
Analytical		

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/

FOLAREMI ADEYEMO
03/30/2020 02:03:01 PM