CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214253Orig1s000

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:	April 26, 2021
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 214253
Product Name and Strength:	Levothyroxine sodium injection, 100 mcg/mL
Applicant/Sponsor Name:	Custopharm, Inc
OSE RCM #:	2020-1570-2
DMEPA Safety Evaluator:	Melina Fanari, RPh
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 21, 2021 for Levothyroxine sodium injection. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Levothyroxine sodium injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that Office of Pharmaceutical Quality forwarded to the Applicant to revise the product strength presentation from [redacted] (b) (4) to 100 mcg/mL.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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/s/

HEATHER G BUCK
03/10/2021 09:58:59 AM

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

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

Memorandum

Date: March 09, 2021

To: Shivangi R. Vachhani, M.D., Medical Officer
Division of General Endocrinology (DGE)

Linda Galgay, RPM, DGE

Monika Houstoun, Associate Director for Labeling

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for LEVOTHYROXINE SODIUM injection, for intravenous use

NDA 214253

In response to DEG's consult request dated August 6, 2020, OPDP has reviewed the proposed product labeling (PI) LEVOTHYROXINE SODIUM injection, for intravenous use.

PI/PPI/C-C: OPDP's comments on the proposed labeling are based on the draft materials sent by DGE on March 3, 2021, and are provided below.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
03/09/2021 07:44:50 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Division of Pediatric and Maternal Health Review

Date: 1/13/2021 **Date consulted:** 8/6/2020

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

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

To: Division of General Endocrinology (DGE)

Drug: Levothyroxine Sodium Injection

NDA: 214253

Applicant: Custopharm, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: For the treatment of myxedema coma

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 214253
- DGE consult form for DPMH, DARRTS Reference ID 4653124

- DPMH review of levothyroxine oral solution, NDA 214047, by Wenjie Sun, MD, on September 1, 2020, DAARTS Reference ID 4664627[1]
- DPMH review of Levothyroxine Sodium injection, NDA 210632, by Christos Mastroyannis, MD, on March 7, 2019, DARRTS Reference ID 4400668[2]
- DPMH review of Tirosint-Sol, NDA 206977, by Jacqueline Spaulding, MD, on November 11, 2016, DARRTS Reference ID 206977[3]

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 July 17, 2020, the applicant (Custopharm, Inc.) submitted a new NDA 214253 for Levothyroxine Sodium Injection for approval. The Division of General Endocrinology (DGE) consulted the Division of Pediatric and Maternal Health (DPMH) on August 6, 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 July 17, 2020 Custopharm, Inc. submitted a new formulation for levothyroxine sodium injection, 100mcg/mL, NDA 214253, for the treatment of myxedema coma.
- 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), Levothyroxine Sodium for Injection (NDA 202231), approved June 24, 2011.

Drug Characteristics

Levothyroxine Characteristics[4]

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

[1] The levothyroxine oral solution 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 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.
[3] 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.
[4] Levothyroxine Sodium Injection proposed package insert

	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	T4: 6-8 days in euthyroid patients, 3-4 days in hyperthyroidism, 9-10 days in hypothyroidism; T3: ≤ 2 days in euthyroid patients,
Protein Binding	>99%
Bioavailability	100%
Serious Adverse Reactions	Over treatment may cause cardiac adverse reactions in the elderly and in patients with underlying cardiovascular disease. Levothyroxine Sodium for Injection therapy for patients with previously undiagnosed endocrine disorders, including adrenal insufficiency, hypopituitarism, and diabetes insipidus, may worsen symptoms of these endocrinopathies.

Current State of the Labeling for the approved RLD, Levothyroxine Sodium for Injection

- Approved labeling is in Physician Labeling Rule (PLR) format, but not PLLR format.
- There is a boxed warning: not treatment of obesity or for weight loss.
- There is no contraindication for use.

Subsection 8.1 Pregnancy notes the following:

Pregnancy Category A

"There are no reported cases of Levothyroxine Sodium for Injection used to treat myxedema coma in patients who were pregnant or lactating. Studies in pregnant women treated with oral levothyroxine to maintain a euthyroid state have not shown an increased risk of fetal abnormalities. Therefore, pregnant patients who develop myxedema should be treated with Levothyroxine Sodium for Injection as the risk of non-treatment is associated with a high probability of significant morbidity or mortality to the maternal patient and the fetus."

Subsection 8.2 Labor and Delivery notes the following:

"Patients in labor who develop myxedema have not been reported in the literature. However, patients should be treated with Levothyroxine Sodium for Injection as the risk of non-treatment is associated with a high probability of significant morbidity or mortality to the maternal patient and the fetus."

Subsection 8.3 Nursing Mothers notes the following:

"Adequate replacement doses of thyroid hormones are required to maintain normal lactation. There are no reported cases of Levothyroxine Sodium for Injection used to treat myxedema coma in patients who are lactating. However, such patients should be treated with Levothyroxine Sodium for Injection as the risk of nontreatment is associated with a high probability of significant morbidity or mortality to the nursing patient."

- There are no existing pregnancy testing/contraception recommendations.

- There are known drug-drug interactions with hormonal contraceptives. Subsection 7.7 notes:
  "Changes in thyroxine binding globulin (TBG) concentration must be considered when interpreting levothyroxine and triiodothyronine values, which necessitates measurement and evaluation of unbound (free) hormone and/or determination of the free levothyroxine index. Pregnancy, infectious hepatitis, estrogens, estrogen containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations."

REVIEW

PREGNANCY

Condition: Myxedema coma and pregnancy[5]

Myxedema coma, a rare neurological condition, is defined as severe hypothyroidism leading to decreased mental status, hypothermia, and other symptoms related to slowing of function in multiple organs. It is a medical emergency with a high mortality rate. Fortunately, it is now a rare presentation of hypothyroidism, likely due to earlier diagnosis as a result of the widespread availability of thyroid-stimulating hormone (TSH) assays. Myxedema coma still has a 20–40% mortality rate, despite intensive treatment, and outcomes are independent of the T4 and TSH levels. Clinical manifestations include reduced level of consciousness, sometimes associated with seizures, as well as the other features of hypothyroidism. Hypothermia can reach 23°C (74°F).

There may be a history of treated hypothyroidism with poor compliance, or the patient may be previously undiagnosed. Myxedema coma almost always occurs in the elderly, (older women being most often affected)[6] and is usually precipitated by factors that impair respiration, such as drugs (especially sedatives, anesthetics, and antidepressants), pneumonia, congestive heart failure, myocardial infarction, gastrointestinal bleeding, or cerebrovascular accidents. Sepsis should also be suspected; hypoglycemia and dilutional hyponatremia also contribute to the development of myxedema coma.[7] Myxedema coma is an endocrine emergency that should be managed aggressively as the mortality rate is high.[8] Older age, cardiac complications, reduced consciousness, need for mechanical ventilation, persistent hypothermia, and sepsis were predictive of mortality.[9, 10] Myxedema coma is a rare entity among pregnant women with fewer than 40 cases reported since 1897.[11, 12]

Nonclinical Experience

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

[6] Ono Y, Ono S, Yasunaga H, et al. Clinical characteristics and outcomes of myxedema coma: Analysis of a national inpatient database in Japan. J Epidemiol 2017; 27:117.

[7] Harrison's Internal Medicine, Chapter 376: Hypothyroidism

[8] Rossn DS: Uptodate Myxedema coma, May 22, 2017

[9] Yamamoto T, Fukuyama J, Fujiyoshi A. Factors associated with mortality of myxedema coma: report of eight cases and literature survey. Thyroid 1999; 9:1167.

[10] Dutta P, Bhansali A, Masoodi SR, et al. Predictors of outcome in myxoedema coma: a study from a tertiary care centre. Crit Care 2008.

[11] Yamamoto et al.

[12] Dutta et al.

Animal reproduction studies have not been conducted with levothyroxine.

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 202231. The applicant only submitted one nonclinical protein binding study, no clinical study was submitted.

Review of Literature

Applicant's Review of Literature

The applicant conducted an online search of published literature regarding the use of levothyroxine injection in pregnancy. The applicant was unable to locate any publications regarding the use of levothyroxine injection in pregnancy. For a full account of applicant's submission of review of literature in pregnancy, see applicant's submission on July 17, 2020, Module 1.2, under "Cover Letter" (sequence number 0002).

The applicant concluded that although there is no literature on the use of levothyroxine injection in pregnancy, there are literature on use of levothyroxine in pregnancy.

> "Myxedema coma is a relatively rare life-threatening condition. Although 80% cases occur in women > 60 years of age, myxedema coma can occur in younger patients as well, with 36 documented cases reported during pregnancy.[13,14] Delaying treatment of myxedema coma in a pregnant individual would increase the risk of maternal and fetal harm."

DPMH's Review of Literature

In the 2020 DPMH review of levothyroxine by Wenjie Sun, MD,[15] DPMH noted:

> "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 especially in pregnancy."

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 March 2020, using Embase, Pubmed, Micromedex,[16] ReproTox,[17] TERIS,[18] and Shepard's.[19] Search terms used were

[13] Patel, S. et al. 1991. A pre-eclamptic-like syndrome associated with hypothyroidism during pregnancy. Quarterly J of Medicine 289:435-441.

[14] Wartofsky, L and Klubo-Gwiezdzinska, J. 2019. Myxedema Coma in M. Luster et al. (eds.), The Thyroid and Its Diseases, Springer Nature.

[15] DPMH review of levothyroxine oral solution, NDA 214047, by Wenjie Sun, MD, on September 1, 2020, DAARTS Reference ID 4664627

[16] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 8/10/2020.

[17] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 8/10/2020.

[18] Teris database, Truven Health Analytics, Micromedex Solutions. Accessed 8/10/2020.

[19] 2020 Shepard's: A Catalog of Teratogenic Agent. Accessed 8/10/2020.

"levothyroxine" AND "pregnancy," "levothyroxine" AND "pregnancy" AND "fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage." No additional articles were found.

There has been no change in levothyroxine pregnancy information at reference sites Micromedex,[16] ReproTox,[17] TERIS[18] and Shepard's[19] since the last DPMH review.

Reviewer comment:
The applicant provided an adequate review of published literature regarding levothyroxine use in pregnancy. Overall, published studies did not show an increase in the rate of miscarriage, malformations or adverse maternal or fetal outcomes.[20,21,22,23,24,25,26] *No additional studies were found regarding use of levothyroxine in pregnancy; therefore, this reviewer concurs with DPMH's previous conclusion that 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, and that levothyroxine replacement is necessary in pregnant women with hypothyroidism.*

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.

Review of Literature

Applicant's Review of Literature

The applicant conducted an online search of published literature regarding the use of levothyroxine during lactation. For a full account of applicant's submission of review of literature in lactation, see applicant's submission on July 17, 2020, Module 1.2, under "Cover Letter" (sequence number 0002).

[20] Heinonen OP et al: Birth Defects and Drugs in Pregnancy. Littleton: Publishing Sciences Group. 1977: 388-400.
[21] 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.
[22] Turunen S, et al. Pregnancy and perinatal outcome among hypothyroid mothers: A population-based cohort study. Thyroid 2019 29;1: 135-141.
[23] 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
[24] 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.
[25] 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.
[26] Maraka S, et al. Effects of Levothyroxine Therapy on Pregnancy Outcomes in Women With Subclinical Hypothyroidism. Thyroid 2016;26(7):980-6.

The applicant noted:

> "Thyroxine is known to be transferred to breast milk during treatment for hypothyroidism.[27] Limited data on exogenous replacement doses of levothyroxine during breastfeeding indicate no adverse effects in infants.[28] In a telephone follow-up study, five nursing mothers reported taking levothyroxine; the mothers reported no adverse reactions in their infants.[29] The American Thyroid Association recommends that subclinical and overt hypothyroidism should be treated with levothyroxine in lactating women seeking to breastfeed.[30] In a clinical study of the maternal impacts of untreated hypothyroidism decreased lactation was reported in approximately 19% of the pregnancies with hypothyroidism."[31]

The applicant concluded:

> "Published data have identified the presence of levothyroxine in breast milk following oral levothyroxine treatment. While no adverse effects on the breastfed infant or maternal milk production have been reported from levothyroxine oral treatment, there currently is insufficient information to determine the full potential effects of Levothyroxine Sodium Injection."

DPMH's Review of Literature

In the 2020 DPMH review of levothyroxine by Wenjie Sun, MD,[32] DPMH noted:

> "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."

DPMH conducted an updated published literature review, since 2020, in PubMed and Embase using the search terms "levothyroxine" AND "lactation" and "levothyroxine" AND "breastfeeding"; no additional articles were found.

[27] Wassenaer, A. et al. 2002. The quantity of thyroid hormone in human milk is too low to influence plasma thyroid hormone levels in the very preterm infant. Endocrinology 56:621-627

[28] Abbassi, V and Stenour, T. 1980. Successful diagnosis of congenital hypothyroidism in four breast-fed neonates. Brief Clin and Lab Obs. 97:259-261

[29] Ito, S. et al. 1993. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. Am J Obstet Gynecol. 168:1393-1399.

[30] Alexander, E. et al. 2017. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 27: 315-389.

[31] Buckshee, K. et al. 1992. Hypothyroidism complicating pregnancy. Aust NZ J Obstet Gynaecol. 32:240.

[32] DPMH review of levothyroxine oral solution, NDA 214047, by Wenjie Sun, MD, on September 1, 2020, DAARTS Reference ID 4664627

There are no new updates on Micromedex,[33] Lactmed,[34] Brigg's,[35] and Hale[36] since the last DPMH review. All reference sites listed above consider levothyroxine as "breastfeeding 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.[37,38,39,40,41]

Overall, the applicant provided an adequate review of published literature regarding levothyroxine 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.

Review of Literature

Applicant's Review of Literature

The applicant conducted an online search of published literature on levothyroxine use and fertility. For a full account of applicant's submission of review of literature in lactation, see applicant's submission on July 17, 2020, Module 1.2, under "Cover Letter" (sequence number 0002). The applicant did not identify any human studies that examined levothyroxine sodium injection and its effect on fertility in females and males of reproductive potential.

[33] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 8/11/2020.
[34] 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 8/11/20.
[35] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 8/11/20
[36] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.
[37] Sack J, Amado O, Lunenfeld B. Thyroxine concentration in human milk. J Clin Endocrinol Metab 1977; 45:171-3
[38] 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.
[39] 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.
[40] 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.
[41] Jansson L, Ivarsson S, Larsson I, Ekman R. Tri-iodothyronine and thyroxine in human milk. Acta Paediatr Scand 1983; 72:703-5.

DPMH's review of literature

In the 2020 DPMH review of levothyroxine by Wenjie Sun, MD,[42] DPMH 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 2020, using Embase, Pubmed, Micromedex,[43] ReproTox,[44] and TERIS.[45] Search terms used were "levothyroxine AND reproduction," "levothroyxine AND infertility," and "levothyroxine AND contraception."

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

There are no new updates on ReproTox.[45]

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 Drug-Laboratory Test Interactions

> Pregnancy, infectious hepatitis, estrogens, estrogen containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations.

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. (b) (4) [redacted]

Overall, the applicant provided an adequate review of published literature regarding levothyroxine 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.

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[42] DPMH review of levothyroxine oral solution, NDA 214047, by Wenjie Sun, MD, on September 1, 2020, DAARTS Reference ID 4664627

[43] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 8/11/2020

[44] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 8/11/2020.

[45] Teris database, Truven Health Analytics, Micromedex Solutions, Accessed 8/11/2020

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 especially in pregnancy.

Levothyroxine is used in females of reproductive potential and in pregnancy. There is no safety concern for levothyroxine 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 effects from levothyroxine replacement in mothers of breastfeeding infants.

Levothyroxine has been used in females of reproductive potential and in lactating women for several decades. There is no safety concern for levothyroxine 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.

(b) (4)

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The clinical data in pregnant women treated with oral levothyroxine to (b) (4) (b) (4) major birth defects, miscarriage, or adverse maternal or fetal outcomes. There is no available data on the use of Levothyroxine Sodium Injection in pregnant

women. There are risks to the mother and fetus associated with myxedema coma in pregnancy *(see Clinical Considerations)*. (b) (4)

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 Embryo/Fetal Risk

Myxedema coma is a medical emergency that can be fatal, if left untreated. Delaying treatment in pregnant women with myxedema coma increases the risk of maternal and fetal morbidity and mortality. Life-sustaining therapy for pregnant women should not be withheld due to potential concerns regarding the effects of Levothyroxine Sodium Injection on the fetus.

8.2 Lactation

Risk Summary

Published studies report that levothyroxine is present in human milk following the administration of oral levothyroxine. No adverse effects on the breastfed infant have been reported and there is no information on the effects of levothyroxine on milk production. There is no available data with use of Levothyroxine Sodium Injection in lactating women. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Levothyroxine Sodium Injection and any potential adverse effects on the breastfed infant from Levothyroxine Sodium Injection or from the underlying maternal condition.

APPENDIX A. Summary of Studies in previous DPMH Reviews of Levothyoxine use in Pregnancy[46][47] (Reviewer's Table)

Publication; author/date/Country	Type of study	Population/control/n/disease	N	Exposure time	Outcomes	Comments
Nergo et al.[48] (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.[49] (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.[50] (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	14067 with birth defect (316 with thyroid disease)	3-month prior pregnancy and pregnancy	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)

[46] DPMH review of NDA 206977 on November 11, 2011, DARRTS Reference ID 206977
[47] DPMH review of levothyroxine oral solution, NDA 214047, by Wenjie Sun, MD, on September 1, 2020, DAARTS Reference ID 4664627
[48] 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
[49] 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.
[50] 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.

		thyroid disease) randomly select from hospital records		: thyroid 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.	-Cons: retrospective at risk for recall bias; lack of thyroid function data; drug effect cannot be separated from disease (such as effect of autoantibodies)
Hallengren B, et al.[51] (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.[52] (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.[53] (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.[54] (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	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

[51] 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.

[52] 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

[53] 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.

[54] 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.

		subpopulation was linked to the Danish EUROCAT congenital anomaly register.				medication resulted in euthyroid state is unknown.
Howley MM, et al.[55] (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)
Sun X, et al.[56] (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.[57] (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 mIU/L) or TAI improve pregnancy continuation rate in recurrent pregnancy loss (RPL) patients.	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 assumption that treatments of other concurrent factors contributing to RPL were effective; non-adherence was not corrected.

[55] 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.

[56] 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).

[57] 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.

Dhillon-Smith, et al.[58] (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 □g 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.[59] (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.[60] (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) -thyroid peroxidase antibody positivity vs euthyroid women, 6/6% vs 5%, OR 1.33 (95% CI, 1.15-1.56).	L-only 5 of 19 studies reported TgAb; causality cannot be determined from observational studies.
Akhtar MA, et al.[61] (2019) UK	Cochrane Database Review	- evaluate the efficacy and harms of levothyroxine replacement in subfertile women with SCH or euthyroid women with TAI	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.	

[58] 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)

[59] 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)

[60] 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)

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

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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:	January 8, 2021
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 214253
Product Name and Strength:	Levothyroxine sodium injection, 100 mcg/mL
Applicant/Sponsor Name:	Custopharm, Inc.
OSE RCM #:	2020-1570-1
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 December 17, 2020 for levothyroxine sodium injection. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for levothyroxine sodium injection (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 December 15, 2020.[a]

2 CONCLUSION

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

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[a] Fanari, M. Label and Labeling Review for levothyroxine sodium injection (NDA 214253). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Dec 15. RCM No.: 2020-1570.

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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:	December 15, 2020
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 214253
Product Name, Dosage Form and Strength:	Levothyroxine sodium injection, 100 mcg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Custopharm, Inc.
FDA Received Date:	August 17, 2020
OSE RCM #:	2020-1570
DMEPA Safety Evaluator:	Melina Fanari, RPh
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the 505(b)(2) NDA approval for levothyroxine sodium injection, the Division of General Endocrinology (DGE) requested that we review the proposed levothyroxine sodium injection 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-N/A
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 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 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. We do not have comments related to the Prescribing Information (PI).

Table 2. Identified Issues and Recommendations for Division of Metabolism and Endocrinology Products (DMEP)

IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration		
1. (b) (4)	(b) (4)	(b) (4)

Table 2. Identified Issues and Recommendations for Division of Metabolism and Endocrinology Products (DMEP)		
IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(b) (4)

Table 3. Identified Issues and Recommendations for Custopharm, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling and Container Label			
1.	NDC number is denoted by a placeholder.	Per 21 CFR 207.33	Revise the placeholder NDC with the entire numerical NDC number.
2.	Expiration date is undefined.	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 3. Identified Issues and Recommendations for Custopharm, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	Units are missing from storage statement.	Minimize confusion and risk for deteriorated drug medication errors due to improper storage.	Revise the store at temperature statement to include the units for each number as follows: 20°C to 25°C (68°F to 77°F)
4.	Usual dosage statement requires revisions.	Per 21 CFR 201.55.	Revise the usual dosage statement to read as follows: "Dosage: See prescribing information."
Container Label			
1.	Net quantity statement is missing.	21 CFR 201.51	Update label to include the net quantity statement and locate away from the product strength, such as to the bottom of the principal display panel.

4 CONCLUSION

Our evaluation of the proposed levothyroxine sodium injection Prescribing Information (PI), container label and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Error! Reference source not found.Table 2 for the Division and Table for the Applicant. We ask that the Division convey Table 3 in its entirety to Custopharm, Inc. 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 levothyroxine sodium injection received on July 17, 2020 from Custopharm, Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Thyquidity and the Listed Drug		
Product Name	Levothyroxine sodium Injection	Levothyroxine sodium for injection; NDA 202231
Initial Approval Date	N/A	1969
Active Ingredient	Levothyroxine sodium	Levothyroxine sodium
Indication	Treatment of myxedema coma	Treatment of myxedema coma
Route of Administration	intravenous	intravenous
Dosage Form	solution	Lyophilized powder
Strength	100 mcg/mL	100 mcg/vial and (b) (4) mcg/vial; Reconstituted concentration of 20 mcg/mL and 100 mcg/mL
Dose and Frequency	300 mcg to 500 mcg intravenous loading dose followed by once daily intravenous maintenance dose between 50 mcg to 100 mcg until patient can tolerate oral therapy	300 mcg to 500 mcg intravenous loading dose followed by once daily intravenous maintenance dose between 50 mcg to 100 mcg until patient can tolerate oral therapy
How Supplied	Single dose 1 mL vials; 100 mcg/mL	Lyophilized powder for injection; 100 mcg/vial and (b) (4) mcg/vial
Storage	Protect from light and store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Discard unused portion.	Protect from light and store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room. Discard unused portion.

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,[a] along with postmarket medication error data, we reviewed the following levothyroxine sodium injection labels and labeling submitted by Custopharm, Inc..

- Container label received on July 17, 2020
- Carton labeling received on July 17, 2020
- Prescribing Information (Image not shown) received on July 17, 2020, available from \\CDSESUB1\evsprod\NDA214253\0002\m1\us\labeling

F.2 Label and Labeling Images

Container Labels

(b) (4)

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

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