CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210632Orig1s000

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 1, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210632
Product Name and Strength:	Levothyroxine Sodium Injection 100 mcg per 5 mL (20 mcg/mL) 200 mcg per 5 mL (40 mcg/mL) 500 mcg per 5 mL (100 mcg/mL)
Applicant/Sponsor Name:	Fresenius Kabi USA LLC
FDA Received Date:	March 27, 2019
OSE RCM #:	2018-1276-3
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Metabolism and Endocrine products requested we review the revised carton and container labels 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 we made during a previous label and labeling review[a] and label and labeling memorandums.[bc]

2 CONCLUSION

We find the revised carton and container labels acceptable from a medication error perspective. We have no additional recommendations at this time.

[a] DeGraw, S. Label and Labeling Review for Levothyroxine Sodium Injection (NDA 210632). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 7. RCM No.: 2018-1276.
[b] DeGraw, S. Review of Revised Label and Labeling Memorandum for Levothyroxine Sodium Injection (NDA 210632). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 14. RCM No.: 2018-1276-1.
[c] DeGraw, S. Review of Revised Label and Labeling Memorandum for Levothyroxine Sodium Injection (NDA 210632). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 21. RCM No.: 2018-1276-2.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

STEPHANIE L DEGRAW
04/01/2019 02:53:05 PM

HINA S MEHTA
04/02/2019 03:13:14 PM

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

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

Memorandum

Date: April 1, 2019

To: Dolly Misra, M.D., Medical Officer
Division of Metabolism and Endocrinology Products (DMEP)

Linda Galgay, Regulatory Project Manager, (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

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

CC: Melinda McLawhorn, Team Leader, OPDP

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

NDA: 210632

In response to DMEP's consult request dated October 24, 2018, OPDP has reviewed the proposed product labeling (PI) and carton container labeling, for LEVOTHYROXINE SODIUM injection, for intravenous use. This is an original NDA.

PI : OPDP's comments on the proposed labeling are based on the draft PI submitted by DMEP via email on March 26, 2019 and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 27, 2019, and we do not have any comments.

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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CHARUNI P SHAH
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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:	March 21, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210632
Product Name and Strength:	Levothyroxine Sodium Injection 100 mcg per 5 mL (20 mcg/mL) 200 mcg per 5 mL (40 mcg/mL) 500 mcg per 5 mL (100 mcg/mL)
Applicant/Sponsor Name:	Fresenius Kabi USA LLC
FDA Received Date:	March 12, 2019
OSE RCM #:	2018-1276-2
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Metabolism and Endocrine products requested we review the revised carton and container labels 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 we made during a previous label and labeling review[a] and label and labeling memorandum.[b]

2 CONCLUSION

We find the revised carton and container labels are unacceptable from a medication error perspective. Specifically, the net quantity is not included on the label. We provide a recommendation below for the Sponsor.

[a] DeGraw, S. Label and Labeling Review for Levothyroxine Sodium Injection (NDA 210632). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 7. RCM No.: 2018-1276.
[b] DeGraw, S. Review of Revised Label and Labeling Memorandum for Levothyroxine Sodium Injection (NDA 210632). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 14. RCM No.: 2018-1276-1.

2.1 RECOMMENDATIONS FOR FRESENIUS KABI USA LLC

We recommend the following be implemented prior to approval of this NDA supplement:

A. Carton and Container Labels

1. As currently presented, the net quantity (i.e., 5 mL) is not included on the principal display panel as required by 21 CFR 201.51. We recommend adding the net quantity "5 mL" before the "Single-Dose Vial" statement.

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/s/

STEPHANIE L DEGRAW
03/21/2019 06:04:39 PM

HINA S MEHTA
03/21/2019 06:31:21 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Labeling Review

From:	Amy M. Taylor, MD, MHS Medical Officer Division of Pediatric and Maternal Health
Through:	Hari Cheryl Sachs, MD Team Leader Division of Pediatric and Maternal Health
NDA Number:	210-632
Sponsor:	Fresenius Kabi USA, LLC
Drug:	Levothyroxine Sodium Injection
Dosage Form and Route of Administration:	Injection, solution for intravenous use
Proposed Adult Indication:	In adult patients for the treatment of myxedema coma
Consult request:	The Division of Metabolic and Endocrine Products (DMEP) requests assistance from the Division of Pediatric and Maternal Health (DPMH) as they review labeling for this NDA.

Background

The sponsor submitted a new NDA 210-632 for Levothyroxine Sodium Injection for the treatment of myxedema coma in adults on June 15, 2018. The product triggers the Pediatric Research Equity Act (PREA) as a new dosage form. The sponsor negotiated an agreed initial pediatric study plan (iPSP) which was accepted by FDA on December 19, 2017. In the agreed iPSP, the sponsor indicated a plan to request a full waiver of pediatric studies required under the PREA because studies are impossible or highly impractical due to the small number of pediatric patients with this condition. There is no change to the plan; the Division agrees with the proposed full waiver because myxedema coma is rare in pediatric patients.

Of note, the sponsor has another levothyroxine product (NDA 202-231) which is a lyophilized powder and was originally approved for marketing on June 24, 2011. The product is indicated for the treatment of myxedema coma in adults.

Selected sponsor proposed pediatric labeling with DPMH suggested edits (strikethroughs represent deletions, and underlining represent additions)

8.4 Pediatric Use

The safety and efficacy of Levothyroxine Sodium Injection have ~~has~~ not been established in pediatric patients.

Additional comment:
Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations. Please refer to the approval letter.

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/s/

AMY M TAYLOR
03/12/2019 02:45:18 PM

HARI C SACHS
03/12/2019 02:48:22 PM
I agree with these recommendations and am also signing on behalf of John J. Alexander, MD, Deputy Director DPMH

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
Telephone: 301-796-2200
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Maternal Health Labeling Review

Date: March 7, 2019 **Date consulted:** October 24, 2018

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., MS, 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 Metabolism and Endocrinology Products (DMEP)

Drug: Levothyroxine Sodium Injection

Class: Thyroid Supplementation

NDA: 210632

Applicant: Fresenius Kabi USA, LLC

Subject: Update of labeling in Pregnancy and Lactation Labeling Rule (PLLR) format

Indication: For the treatment of myxedema coma

Materials Reviewed:

- June 15, 2018, NDA 210632 initial submission for Levothyroxine Sodium Injection
- December 7, 2018, Applicant's "Summary of Literature Search on the Use of Levothyroxine Sodium Injection During Pregnancy , Lactation, and on the Drug's

Potential Effects on Fertility" in response to the Division's Information Request (IR) of November 27, 2018

- Draft Labeling in PLLR format
- October 24, 2018, DMEP's consult request to DPMH for Levothyroxine Sodium Injection labeling review
- November 10, 2016, review by Jacqueline A Spaulding, M.D. in DARRTS and Reference ID: 4009468 of Tirosint-SOL (levothyroxine sodium oral solution), NDA 206977[1]

Consult Question: Assist with Pregnancy and Lactation Labeling Rule (PLLR)

[1] DPMH did not rely on data in the Tirosint-SOL (levothyroxine sodium oral solution) NDA or the Agency's finding of safety and effectiveness for Tirosint-SOL (levothyroxine sodium oral solution) to support labeling sections of this Levothyroxine Sodium Injection NDA. Rather, the cross-reference to the Tirosint-SOL (levothyroxine sodium oral solution) consult is included to avoid duplicating background information and literature relevant to the underlying medical conditions.

INTRODUCTION

On October 24, 2018, the applicant, Fresenius Kabi USA, LLC, submitted an original NDA for Levothyroxine Sodium Injection, NDA 210632, for the treatment of myxedema coma. This is a 505(b)(2) application with listed drug relied upon being Fresenius Kabi's own Levothyroxine Sodium, Powder for intravenous injection (NDA 202231, approved June 24, 2011 for the treatment of myxedema coma.

The proposed labeling of December 7, 2018, is in PLR and PLLR format. DMEP consulted the DPMH on October 24, 2018, to provide input for appropriate labeling of the *Pregnancy* and *Lactation* subsections of Levothyroxine Sodium Injection labeling for accuracy after including the information from the applicant's review of the literature and the company's pharmacovigilance.

BACKGROUND

Regulatory History

The applicant submited labeling in PLR format but was not in PLLR format. On November 27, 2018, DMEP sent an IR to the applicant to provide labeling in PLLR format and support the labeling by providing:

- A review and summary of all available published literature regarding levothyroxine sodium for intravenous injection use in pregnant and lactating women and the effects of levothyroxine sodium for intravenous injection on male and female fertility (including search parameters and a copy of each reference publication).
- A cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present) including the Reference Listed Drug (RLD), NDA 202231.
- A summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval for the RLD.
- An interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry (if applicable).
- A revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

The applicant responded to the IR on December 7, 2018.

Levothyroxine Sodium Drug Characteristics[2]

- Levothyroxine Sodium Injection contains synthetic crystalline levothyroxine (L-thyroxine) sodium salt.
- Molecular weight of 798.85 gr/mol (Da).
- Half-life is 9 to 10 days for people with hypothyroidism and 6 to (b) (4) days for those with normal laboratory results.
- Protein binding is >99% including: thyroxine-binding globulin (TBG), thyroxine binding prealbumin (TBPA) and albumin (TBA).

Myxedema coma

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

[2]Levothyroxine Sodium existing labeling of December 20, 2012

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)[3] 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.[4] Myxedema coma is an endocrine emergency that should be managed aggressively as the mortality rate is high.[5] Older age, cardiac complications, reduced consciousness, need for mechanical ventilation, persistent hypothermia, and sepsis were predictive of mortality.[6,7] Myxedema coma is a rare entity among pregnant women with fewer than 40 cases reported since 1897.[8,9]

[3] 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.
[4] Harrison's Internal Medicine, Chapter 376: Hypothyroidism
[5] Rossn DS: Uptodate Myxedema coma, May 22, 2017
[6] Yamamoto T, Fukuyama J, Fujiyoshi A. Factors associated with mortality of myxedema coma: report of eight cases and literature survey. Thyroid 1999; 9:1167.
[7] Dutta P, Bhansali A, Masoodi SR, et al. Predictors of outcome in myxoedema coma: a study from a tertiary care centre. Crit Care 2008.
[8] Turhan NO, Koçkar MC, Inegol I. Myxedematous coma in a laboring woman suggested a pre-eclamptic coma: a case report. Acta Obstet Gynecol Scand. 2004 Nov;83(11):1089-91
[9] Lachelin GC. Myxoedema and pregnancy. A case report. J Obstet Gynaecol Br Commonw. 1970 Jan; 77(1):77-79.

Current Labeling for Listed Drug Relied Upon, Levothyroxine Sodium Injection[10]

The current labeling for Levothyroxine Sodium Injection is in PLR format and not in PLLR. It states:

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------INDICATIONS AND USAGE----------

Levothyroxine Sodium is an L-thyroxine product. Levothyroxine (T4) Sodium for Injection is indicated for the treatment of myxedema coma.

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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.

8.2 Labor and Delivery

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.

8.3 Nursing Mothers

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or effects on fertility of Levothyroxine Sodium for Injection.

[10] Levothyroxine Sodium Injection labeling, last approved on December 20, 2012

REVIEW

PREGNANCY

Animal Data

There are no animal reproduction studies that have been conducted with levothyroxine.

Review of Literature

Applicant's Review

A literature search was performed by the applicant for use of Levothyroxine Sodium in pregnant women. Medline, Embase database, PubMed, Cochrane Library, & Clinical trail.gov were searched. Search terms include: "Levothyroxine", "L-thyroxine", "Thyroxine", "LT4", "Hypothyroidism", "Myxedema Coma", "Pregnancy", "Intravenous", "Injection" and "Parenteral". No publications of Levothyroxine Sodium for Injection used in patients who were pregnant were identified. The Applicant did not conduct any clinical studies with use of Levothyroxine Sodium injection during pregnancy. Since the application is 505(b)(2) NDA, the Applicant is relying on the Agency's finding of safety and effectiveness for NDA 202231.

DPMH Review

In addition to the search of published literature performed by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for Levothyroxine Sodium and use in pregnancy. ReproTox states "Thyroxine replacement therapy has not been clearly associated with an increased risk of congenital anomalies. Thyroxine insufficiency has a well-defined association with impaired fetal and neonatal development. Adequate replacement of hypothyroid women is recommended to optimize pregnancy outcome. Thyroid hormone use to maintain a condition of euthyroidism in pregnancy allows normal embryo-fetal development, especially of the central nervous system. Treatment of hypothyroidism lowers the chance of miscarriage and premature delivery in pregnant women. followed during pregnancy.[5,11,12] "Most experts agree that adequate hormone replacement during pregnancy minimizes the risk of adverse outcomes and most complications".[13]

Table 1: Pregnancy Complications in 440 Women with Hypothyroidism[19]

	Hypothyroidism (%)	
Complications	Overt (n=112)	Subclinical (n=328)
Preeclampsia	32	8
Placenta Abruption	8	1
Cardiac Dysfunction	3	2
Birth Weight <2000g	33	32
Stillbirths	9	3

[11] Harrison's Principles of internal medicine. Hypothyroidism

[12] Lowell DE et al: Hypothyroidism complicating pregnancy. Obstet Gynecol 72:108-112, 1988

[13] William's Obstetrics. Hypothyroidism

The Collaborative Perinatal Project did not identify any significant associations between specific birth defects and thyroxine exposure during the first trimester or at any time during pregnancy.[14] . A registry study involving 623 pregnancies with 1st trimester exposure to levothyroxine did not identify an increased risk of congenital defects.[15] The National Birth Defects Prevention Study, a large population-based, case-control study, reported an increased risk for hydrocephaly (OR 3.1; 1.6-5.2) in 2009 when thyroxine was used during the periconceptional period.[16] GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation report that "Levothyroxine (T4) is compatible with all stages of pregnancy. Untreated or undertreated maternal hypothyroidism is associated with low birth weight secondary to medically indicated preterm delivery, preeclampsia or placental abruption, and with lower neuropsychological development of their offspring." No reports of myxedema coma were indetified. Because myxedema coma is a medical emergency with high mortality rates, it should be treated as aggressively as possible without delay.

Pharmacovigilance Review

As per the applicant, (b) (4) was searched on November 27, 2018 for all case reports for Levothyroxine from the approval date of NDA 202231, June 24, 2011 to 27 Nov 2018. A total of 42 case reports from both spontaneous and literature sources were identified. Of these 42 case reports, there were 26 females, 10 males and in 6 cases, ages were not reported. There were 15 female patients in the age of reproductive potential (e.g., 15 to 44 years). None of the reports indicated that the patient was pregnant or lactating. Furthermore, there were no reports indicating impaired fertility. In the seven years since the approval of NDA 202231, there have been no reports of adverse events occurring in pregnant and lactating women.

There is no current or past pregnancy registry for Levothyroxine Sodium Injection.

Utilization Review

Because there are no reported cases of use of intravenous levothyroxine in pregnant or lactating women and pharmacovigilance did not identify any cases of use of this product in the pregnant or lactating population, the applicant (b) (4) "

Reviewer Comment

Utilization review in addition to labeled indication usage provides information for any additional usage due to off label use. Safety of a drug product includes both labeling and off label use. Therefore, this reviewer does not agree with the applicant's statement. (b) (4)

Summary

Myxedema coma occurs mostly in older women with hypothyroidism or other precipitating conditions. Because it has a high mortality rate, it is a medical emergency that should be treated

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[14] Heinonen OP et al: Birth Defects and Drugs in Pregnancy. Littleton: Publishing Sciences Group. 1977: 388-400.
[15] 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.
[16] Browne ML, Rasmussen SA, Hoyt AT, 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.
[17] (b) (4)

aggressively. Delaying treatment in pregnant women with myxedema coma may increase the risk of maternal and fetal mortality. Life-sustaining therapy for the pregnant woman should not be delayed for a life-threatening condition due to potential risks from levothyroxine use. Treatment of hypothyroidism in pregnancy is also 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.

LACTATION

Animal Data

There are no animal lactation studies that have been conducted with levothyroxine.

Review of Literature

The applicant states that there were no publications with Levothyroxine Sodium Injection and lactation. DPMH review of the literature also failed to produce any publications. A woman in myxedema coma will not be able to breastfeed. After recovery from myxedema coma sufficient to allow for breastfeeding, the intravenous injection will generally be converted to oral preparations. Oral levothyroxine has been reviewed by Dr. Jacqueline Spaulding for NDA 206977, in DARRTS and dated November 11, 2016, Reference ID: 4009468. As GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation state: "Levothyroxine (T4) is present in breast milk in low concentrations." Two reports have claimed that sufficient quantities are present to partially treat neonatal hypothyroidism.[18,19] GG Briggs and RK Freeman conclude "Levothyroxine breast milk levels, as determined by modern laboratory techniques, 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.[20] The American Academy of Pediatrics classifies levothyroxine as compatible with breastfeeding.[21] ToxNet states "Levothyroxine (T4) is a normal component of human milk. Limited data on exogenous replacement doses of levothyroxine during breastfeeding indicate no adverse effects in infants." The American Thyroid Association recommends that subclinical and overt hypothyroidism should be treated with levothyroxine in lactating women seeking to breastfeed.[22] Effects of exogenous thyroid hormone administration to mothers on their infant have not been reported.

Summary

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.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Animal Data

There have been no animal studies conducted to evaluate the effects of levothyroxine on

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[18] Sack J, Amado O, Lunenfeld B. Thyroxine concentration in human milk. J Clin Endocrinol Metab 1977;45:171-3.
[19] Bode HH, Vanjonack WJ, Crawford JD. Mitigation of cretinism by breastfeeding. Pediatrics 1978;62:13-6
[20] Franklin R, O'Grady C, Carpenter L. Neonatal thyroid function: comparison between breast-fed and bottle-fed infants. J Pediatr 1985;106:124-6
[21] Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. Pediatrics 2001;108:776-89.
[22] Alexander EK, Pearce EN, Brent GA et al. 2016 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum. Thyroid. 2017;27:315-89

fertility.

Review of Literature

The applicant did not identify any reports of Levothyroxine Sodium injection and its effects on Females and Males of reproductive potential. DPMH also did not identify any publications on Levothyroxine Sodium injection and its effects on Females and Males of reproductive potential. Oral levothyroxine has been reviewed by Dr. Jacqueline Spaulding for NDA 206977, in DARRTS and dated November 11, 2016, Reference ID: 4009468 and concludes that "There is no evidence in the literature to suggest that levothyroxine adversely affects male or female fertility".

Summary

There are no human data available on the effect of levothyroxine on male or female fertility. Therefore, Section 8.3, Females and Males of Reproductive Potential, will not be included in Levothyroxine Sodium injection labeling, because there is nothing to be reported. Contraception and pregnancy testing during treatment with levothyroxine are not recommended.

CONCLUSIONS

Levothyroxine Sodium injection labeling has been revised to comply with the PLLR. A review of the literature for relevant data revealed no safety concerns with Levothyroxine Sodium injection use in pregnancy and lactation. Because myxedema coma has a high incidence of mortality, it is a medical emergency that should be treated aggressively immediately as it is diagnosed. Delaying treatment in pregnant women with myxedema coma may increase the risk of maternal and fetal mortality.

DPMH has the following recommendations for the Levothyroxine Sodium injection labeling:

- Pregnancy, Subsection 8.1
  The "Pregnancy" subsection of Levothyroxine Sodium injection labeling was formatted in the PLLR format to include: "Risk Summary", "Clinical Considerations" and "Data" headings.
- Lactation, Subsection 8.2
  The "Lactation" subsection of Levothyroxine Sodium injection labeling was formatted in the PLLR format to include the "Risk Summary" heading.
- Females and Males of Reproductive Potential, Subsection 8.3 is omitted.

RECOMMENDATIONS

The below includes DPMH recommendations for the Levothyroxine Sodium injection labeling for compliance with the PLLR. DPMH presented these recommendations to the Division on February 27, 2019. DPMH refers to the final NDA action for final labeling.

PRESCRIBING INFORMATION

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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. There are no available data with 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)*. Animal reproduction studies have not been conducted with levothyroxine sodium.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. 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

Myxedema coma is a medical emergency (b) (4) which 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 the pregnant woman should not be withheld.

8.2 Lactation

Risk Summary

Published studies report that levothyroxine is present in human milk following the administration of oral levothyroxine. (b) (4) on the breastfed infant (b) (4) 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 and any potential adverse effects on the breastfed infant from levothyroxine or from the underlying maternal condition.

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/s/

CHRISTOS MASTROYANNIS
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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 14, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210632
Product Name and Strength:	Levothyroxine Sodium Injection 100 mcg per 5 mL (20 mcg/mL) 200 mcg per 5 mL (40 mcg/mL) 500 mcg per 5 mL (100 mcg/mL)
Applicant/Sponsor Name:	Fresenius Kabi USA LLC
FDA Received Date:	December 28, 2018
OSE RCM #:	2018-1276-1
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Metabolism and Endocrine products requested we review the revised carton and container labels for Levothyroxine Sodium Injection 100 mcg per 5 mL, 200 mcg per 5 mL, and 500 mcg per 5 mL (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton and container labels are unacceptable from a medication error perspective. Specifically, we recommend increasing the font of the single-dose vial statement. In addition, we note the location of the 2D matrix barcode is not indicated on the carton labeling. We provide specific recommendations below for the Sponsor.

[a] DeGraw, S. Label and Labeling Review for Levothyroxine Sodium Injection (NDA 210632). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 7. RCM No.: 2018-1276.

2.1 RECOMMENDATIONS FOR FRESENIUS KABI USA LLC

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels and Carton Labeling

1. As currently presented, the "(b) (4)" statement may be overlooked. Therefore, consider revising the statement "(b) (4)" to read "Single-Dose Vial – Discard Unused Portion" and increasing the prominence of this statement (e.g., enlarge the font size, use a bolded font) to minimize the risk of the entire contents of the vial being given as a single dose in error or use of the remaining vial contents for a second dose.

B. Carton Labeling

1. As currently presented, the inclusion and placement of the product identifier in a 2D data matrix barcode format is not indicated. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[b] A product identifier is a standardized graphic that includes the product's standardized numerical identifier (composed of the NDC and a unique alphanumeric serial number), lot number, and expiration date, in both human- and machine-readable formats. The product identifier data is specifically required under section 582(a)(9) of the FD&C Act to be in a "2-dimensional data matrix barcode" for packages and in a "linear or 2-dimensional data matrix barcode" for homogenous cases, which can be verified using "human-readable or machine-readable methods." Section 582(b)(2)(A) of the FD&C Act requires manufacturers and repackagers, respectively, to "affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce" beginning November 27, 2017, and November 27, 2018, respectively. Therefore, include a 2D data matrix barcode containing the required product identifier information in addition to the current linear barcode.

[b] https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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:	November 7, 2018
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210632
Product Name and Strength:	Levothyroxine Sodium Injection 100 mcg per 5 mL (20 mcg/mL) 200 mcg per 5 mL (40 mcg/mL) 500 mcg per 5 mL (100 mcg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fresenius Kabi USA LLC
FDA Received Date:	June 15, 2018
OSE RCM #:	2018-1276
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

The Division of Hematology products requested a review of the Prescribing Information (PI) and carton labeling and container labels submitted under NDA 210632 for Levothyroxine Sodium Injection by Fresenius Kabi on June 15, 2018. This application is a 505(b)(2) and the reference drug is levothyroxine sodium for injection, NDA 202231.

1.1 REGULATORY HISTORY

Levothyroxine Sodium for Injection was a marketed unapproved drug used for the treatment of myxedema coma and other forms of hypothyroidism in which oral levothyroxine administration is not feasible. On December 18, 2006, the FDA issued a warning letter to the manufacturer (APP Pharmaceuticals, LLC) stating that in order to lawfully market this product, it will need to submit a New Drug Application. On August 30, 2010, APP Pharmaceuticals submitted NDA 202231 for Levothyroxine Sodium for Injection 100 mcg per vial, 200 mcg per vial, and 500 mcg per vial for the treatment of myxedema coma. The application was approved on June 24, 2011.

Fresenius Kabi submitted NDA 210632 on June 15, 2018, for Levothyroxine Sodium Injection 100 mcg per 5 mL, 200 mcg per 5 mL, and 500 mcg per 5 mL for the treatment of myxedema coma. This product is available as a preservative-free solution, and therefore, does not require reconstitution or further dilution before administration.

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
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G

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 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed PI, container labels, and carton labeling for Levothyroxine Sodium Injection to determine if the proposed labels and labeling adequately mitigate medication use errors.

The proposed PI and container labels and carton labeling for Levothyroxine Sodium Injection may be improved to minimize the potential for medication errors to occur. We provide specific recommendations in Section 4.1 and Section 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed the Prescribing Information, container label, and carton labeling identified areas to improve clarity of the labeling as it relates to NDC numbers, strength statement, and storage of the product. We provide specific recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Highlights: Dosage Forms and Strengths
    a. To increase readability, a unit-of-measure should follow each numeric dose designation. For example, revise "(b) (4) " to (b) (4) ."
    b. Route of administration should be clearly stated without the use of abbreviations to prevent confusion. Consider replacing "(b) (4) " with "do not add to (b) (4) *intravenous* fluids."

2. Section 2: Dosage and Administration
    a. Section 2.1: Dosage
        i. To increase readability, a unit-of-measure should follow each numeric dose designation. For example, revise "(b) (4) " to (b) (4) " and "(b) (4) " to "(b) (4) ."
        ii. Consider adding recommendations for administration of the product (e.g., intravenous bolus).
    b. Section 2.3: Administration
        i. Route of administration should be clearly stated without the use of abbreviations to prevent confusion. Consider replacing "(b) (4)

[redacted] with "do not add to [redacted] *intravenous* fluids."

3. Section 3: Dosage Forms and Strengths
    a. Consider adding information about color (i.e., clear solution) and other identifying characteristics to facilitate identification of the dosage form.
        i. Revise statement to read "Levothyroxine Sodium Injection is supplied as a *clear, colorless* solution [redacted] single-dose [redacted] vials: 100 mcg per 5 mL (20 mcg per mL), 200 mcg per 5 mL (40 mcg per mL), and 500 mcg per 5 mL (100 mcg per mL)."

4. Section 16.1: How Supplied
    a. Consider adding information about color (i.e., clear solution) and other identifying characteristics to facilitate identification of the dosage form.
        i. Revise statement to read "Levothyroxine Sodium Injection is available *as a clear, colorless solution* [redacted]"

4.2 RECOMMENDATIONS FOR FRESENIUS KABI USA LLC

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The similarity of the product code numbers in the NDC number has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (i.e., -(b) (4)-). Revise the product code in the NDC numbers to ensure that the middle 3 digits are different between the strengths. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their font size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXXX-**XXX**-XX.[a]

2. As currently presented, the strength per total volume statement (e.g., 100 mcg per 5 mL) and the strength per milliliter statement (e.g., 20 mcg per mL) appear as equal size. A number of overdoses have occurred with small-volume parenteral products because of healthcare practitioner and patient failure to determine the total amount of drug in the container.[a] To avoid such confusion, consider increasing the size of the strength per total volume in relation to the strength per milliliter. For example:

   100 mcg per 5 mL
   (20 mcg per mL)

3. We recommend revising the statement "(b) (4)" to read "Usual dosage: See prescribing information" per 21 CFR 201.55.

4. As currently present, the container labels and carton labeling state "(b) (4)" rather than the full statement that is in section 16.2, Storage and Handling of the PI that reads "protect from light in original vial in a carton." Revise the statement on the labels and labeling to align with the statement in the PI.

[a] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

B. Container Labels

1. Revise the "each mL" statement to accurately reflect the contents of the vial per mL.
    a. For example, revise:
        i. The (b) (4) to read "Each mL contains 20 mcg."
        ii. The (b) (4) to read "Each mL contains 40 mcg."
        iii. The (b) (4) to read "Each mL contains 100 mcg."

2. As currently presented, the format for the expiration date is not indicated. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use.
    a. We recommend 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.

3. Ensure the lot number is clearly differentiated from the expiration date[b] and that there are no other numbers located in close proximity to the lot number or expiration date where they can be confused with one another.[c]

C. Carton Labeling

1. The inclusion and placement of a lot number and expiration date is not indicated. Please confirm the inclusion and location of both items. We recommend 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

[b] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

[c] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

2. Revise the "(b) (4)" statement to "each mL contains" to reflect the contents of the vial per mL.

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Levothyroxine Sodium Injection received on June 15, 2018 from Fresenius Kabi USA LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Levothyroxine Sodium Injection and the Listed Drug		
Product Name	Levothyroxine Sodium Injection	Levothyroxine Sodium for Injection[d] (NDA 202231)
Initial Approval Date	N/A	June 24, 2011
Active Ingredient	levothyroxine sodium	levothyroxine sodium
Indication	Treatment of myxedema coma	Treatment of myxedema coma
Route of Administration	Intravenous	Intravenous
Dosage Form	Solution for injection	Powder, intravenous
Strength	100 mcg per 5 mL (20 mcg/mL) 200 mcg per 5 mL (40 mcg/mL) 500 mcg per 5 mL (100 mcg/mL)	100 mcg per vial 200 mcg per vial 500 mcg per vial
Dose and Frequency	300 mcg to 500 mcg initially, followed by maintenance doses of 50 mcg to 100 mcg daily, as clinically indicated, until patient can tolerate oral therapy	300 mcg to 500 mcg initially, followed by maintenance doses of 50 mcg to 100 mcg daily, as clinically indicated, until patient can tolerate oral therapy
How Supplied	Single dose vials in cartons	Single dose vials in cartons
Storage	Controlled room temperature	Controlled room temperature
Container Closure	Glass vials closed with gray (b) (4) rubber stoppers, capped with aluminum (b) (4) seals, which are placed in individual cartons Not made with natural rubber latex	Not made with natural rubber latex

[b] Levothyroxine Sodium for Injection [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2012 DEC 20. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202231s003lbl.pdf.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On October 18, 2018, we searched FAERS using the criteria in the table below and identified 521 cases. We individually reviewed the cases and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[e] We narrowed the search results by filtering the reports, reviewing only cases that noted "inject," "intravenous," "IV." We excluded 520 cases because they did not describe errors involving injectable formulations of levothyroxine. The remaining case was also excluded as the report involved a reconstitution error that is not relevant to this NDA as the product does not require reconstitution.

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	10/1/2013 to 10/1/2018
Product Name:	N/A
Product Active Ingredient (PAI):	Levothyroxine; levothyroxine sodium; levothyroxine sodium anhydrous
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	USA

E.2 Results

Our search identified 521 cases, of which none described errors that were relevant for this review.

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[e] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Levothyroxine Sodium Injection labels and labeling submitted by Fresenius Kabi USA LLC.

- Container labels received on June 15, 2018
- Carton labeling received on June 15, 2018
- Prescribing Information (Image not shown) received on June 15, 2018

G.2 Label and Labeling Images

Container Labels

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

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Prescribing Information

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/s/

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11/07/2018

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11/09/2018