CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214253Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Clinical Pharmacology Review
Statistical Review

NDA Multi-disciplinary Review and Evaluation

Application Type	505(b)(2)
Application Number	214253
Priority or Standard	Standard
Submit Date	7/17/20
Received Date	7/17/20
PDUFA Goal Date	5/17/21
Division/Office	Division of General Endocrinology Office of Cardiology, Hematology, Endocrinology, and Nephrology
Review Completion Date	5/6/21
Established Name	levothyroxine sodium injection
(Proposed) Trade Name	N/A
Pharmacologic Class	levothyroxine
Code name	levothyroxine sodium injection
Applicant	Custopharm, Inc.
Formulation	Ready-to-use solution of levothyroxine 100 mcg/mL for intravenous injection
Dosing Regimen	An initial intravenous loading dose of Levothyroxine Sodium Injection between 300 to 500 mcg followed by once daily intravenous maintenance doses between 50 and 100 mcg should be administered, as clinically indicated, until the patient can tolerate oral therapy
Applicant Proposed Indication/Population	Treatment of myxedema coma
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of myxedema coma (SCTID: 21263006)

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OPQ=Office of Pharmaceutical Quality
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DPMH=Division of Pediatric and Maternal Health

Signatures

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ANDA	abbreviated new drug application
ATA	American Thyroid Association
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EDTA	edetate dihydrate
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBECD	sulfobutyl ether beta-cyclodextrin sodium disodium
SGE	special government employee
SOC	standard of care
T3	triiodothyronine
T4	thyroxine
TSH	thyroid stimulating hormone
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Levothyroxine sodium for injection is a synthetic thyroxine hormone proposed for the treatment of myxedema coma. The Applicant submitted a new drug application (NDA) 214253 for a ready-to-use 100 mcg/mL levothyroxine sodium solution in single-dose vials via the 505(b)(2) pathway, relying on the Food and Drug Administration's (FDA) finding of safety and effectiveness of levothyroxine sodium for injection approved under NDA 202231.

The Applicant has proposed a loading dosing of 300 to 500 mcg, followed by once daily maintenance doses between 50 and 100 mcg, as clinically indicated, until the patient can tolerate oral levothyroxine therapy, the same as the reference product.

The injectable formulation of levothyroxine is intended for emergency use for treatment of myxedema coma. Available injectable levothyroxine products include a lyophilized powder for injection that requires reconstitution prior to administration and a ready-to use premixed solution in multi-dose vials.

1.2. Conclusions on the Substantial Evidence of Effectiveness

No clinical studies were submitted to support this NDA. The Applicant is relying on the FDA's findings of safety and effectiveness for levothyroxine sodium for injection marketed by Fresenius Kabi under NDA 202231.

It is well established that myxedema coma is an endocrine emergency associated with profound hypothyroidism that can lead to death if it is left untreated. Myxedema coma is characterized by decompensated mental status and suppressed cardiac, pulmonary, and metabolic functioning. The standard of care treatment for myxedema coma is intravenous (IV) levothyroxine. A loading dose of levothyroxine IV 200-400 mcg is recommended for most patients, followed by a maintenance dose of 1.6 mcg per kilogram per day (mcg/kg/day) until the patient can tolerate oral levothyroxine therapy. Lower doses may be required for smaller patients, elderly patients, or patients with cardiac disease. The goal of therapy is to achieve an improvement in mental status, cardiac function, pulmonary function and metabolic parameters associated with the myxedema state and ultimately, to normalize circulating thyroid hormone levels.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Levothyroxine sodium for injection is a synthetic thyroxine formulation developed to treat myxedema coma, an endocrine emergency associated with severe hypothyroidism. The Applicant submitted NDA 214253 for a ready-to-use 100 mcg/mL levothyroxine sodium solution in single-dose vials via the 505(b)(2) pathway, relying on the FDA's previous findings of safety and effectiveness for levothyroxine sodium for injection approved under NDA 202231.

Myxedema coma is a state of severely decompensated hypothyroidism, resulting from progression of untreated or unrecognized hypothyroidism. Patients in myxedema coma present with multiple organ injuries and progressive mental deterioration that require treatment in an intensive care setting. If untreated, myxedema coma can lead to death.

According to the American Thyroid Association (ATA) guidelines, levothyroxine administered intravenously is the primary treatment for patients in myxedema coma. The ATA guidelines recommend a loading dose of 200-400 mcg of IV levothyroxine in most patients, and a lower loading dose for smaller patients, older patients, or patients with cardiac disease. Subsequently, a daily replacement dose of 1.6 mcg/kg body weight is recommended until there is evidence of clinical improvement and the patient can be switched to oral therapy.

The goal of therapy is to achieve an improvement in mental status, cardiac function, pulmonary function and metabolic parameters initially, and ultimately, to normalize circulating thyroid hormone levels. An increase in levothyroxine dose, with or without addition of liothyronine therapy, may be considered in patients who do not exhibit an improvement in T3 and T4 levels or a reduction in TSH levels.

Levothyroxine therapy is generally well tolerated. Adverse events (AE) typically occur due to over-treatment and are consistent with the signs and symptoms of hyperthyroidism, such as tachycardia, palpitations, cardiac arrhythmias, increased blood pressure, nervousness, diarrhea, abdominal cramps, hyperthermia, heat intolerance, weight loss, increased appetite, and tremors. These AEs will be adequately conveyed in product labeling.

Multiple intravenous levothyroxine and liothyronine products have been approved by FDA for the treatment of myxedema coma. All of the intravenous levothyroxine preparations were approved via the 505(b)(2) NDA or 505(j) Abbreviated New Drug Application (ANDA) pathway, relying upon the efficacy and safety of a previously approved synthetic LT4 or LT3 product. The addition of the intravenous levothyroxine product proposed under NDA 214253 will increase the treatment options for patients with myxedema coma with a formulation that has the additional convenience benefit of a single dose, ready-to-use formulation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Myxedema coma is a state of severely decompensated hypothyroidism. • Clinical signs and symptoms of myxedema coma include multiple organ injuries and progressive mental deterioration. • Patients in myxedema coma often require treatment in an intensive care unit, and if left untreated, myxedema coma can lead to death. • The ATA guidelines recommend intravenous levothyroxine as the first-line treatment of myxedema coma.	Myxedema coma is an endocrine emergency that requires treatment in intensive care unit, and if untreated, can lead to death.
Current Treatment Options	• Multiple injectable levothyroxine and liothyronine products have been approved by the FDA for the treatment of myxedema coma. • The majority of injectable LT4 products are available as a lyophilized powder for injection that require reconstitution prior to administration. This introduces a risk for medical errors and the potential for contamination. Currently, there is one injectable LT4 formulation that is available as a ready-to-use premixed solution.	Multiple injectable levothyroxine products have been approved by the FDA. All of the currently approved injectable levothyroxine products, except one, are available as lyophilized powders for injection that require reconstitution prior to administration. The current armamentarium of injectable levothyroxine products will benefit from approval of a single dose, ready-to-use pre-mixed solution, given the increased convenience to providers and decreased risk for dosing errors and contamination.
Benefit	• Expected benefits of treatment with intravenous levothyroxine in patients with myxedema coma include improvement in mental status, cardiac function, pulmonary function and metabolic parameters, and death prevention.	Intravenous levothyroxine therapy is first-line, life-saving treatment for myxedema coma and results in an improvement in mental status, cardiac function, pulmonary function and metabolic parameters.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Intravenous levothyroxine therapy is generally well-tolerated. • Adverse effects are mostly caused by over-treatment and are consistent with signs and symptoms of hyperthyroidism such as tachycardia, palpitations, increased blood pressure, nervousness, diarrhea, abdominal cramps, hyperthermia, heat intolerance, weight loss, increased appetite, and tremors.	Levothyroxine therapy is generally well tolerated. Adverse effects can occur due to over-treatment and are consistent with the signs and symptoms of hyperthyroidism. These are conveyed in product labeling for all levothyroxine products.

1.4. Patient Experience Data

No patient experience data were submitted in this Application.

2 Therapeutic Context

Hypothyroidism is a condition of low thyroid hormone levels. Myxedema coma is a state of severely decompensated hypothyroidism, resulting from progression of untreated or unrecognized disease.[1] Patients in myxedema coma present with multiple organ injuries and progressive mental deterioration that requires treatment in an intensive care setting. If untreated, myxedema coma can lead to death.

In the United States, the prevalence of hypothyroidism in individuals aged 12 years and older is estimated to be between 0.3% and 9.5%[2,3,4,5]. Women are at a greater risk of developing hypothyroidism compared to men. In one study, the incidence of hypothyroidism was 3.5 per 1000 per year in women, and 0.6 per 1000 per year in men. Hypothyroidism that progresses to myxedema coma is rare. Approximately 80% of cases of myxedema occur in women[6,7]. Older age is also a risk factor, with most cases occurring in patients ≥60 years of age.

Hypothyroidism is characterized by a constitution of non-specific symptoms such as constipation, bradycardia, weight gain, cold sensitivity, dry skin, and fatigue. A patient with long-standing unrecognized or untreated hypothyroidism can present with myxedema coma, which is considered an endocrine emergency. The presence of secondary stressors, such as infection, increase the risk for myxedema coma in at-risk patients. Physical exam findings in a patient in myxedema may include altered mentation, hypothermia, decompensated heart failure, elevated diastolic blood pressure or hypotension, bradycardia, nonpitting edema, delayed reflex relaxation, periorbital edema, alopecia, bladder dystonia and distension, dry or cool skin, abdominal distension, decreased gastrointestinal motility, ileus and fecal impaction.

[1] Rhodes Wall, C. Myxedema Coma: Diagnosis and Treatment. *American Family Physician.* 200; 62(11):2485-2490
[2] Hollowell JG et al. Serum TSH, T(4), and thyroid antibodies in the United states population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *Journal of Clinical Endocrinology and Metabolism.* 2002; 87: 489-499
[3] Canaris GJ et. al. The Colorado thyroid disease prevalence study. *Archives of Internal Medicine.* 2000; 160:526-534
[4] Sawin CT et. al. The aging thyroid. Thyroid deficiency in the Framingham Study. *Archives of Internal Medicine.* 1985;145:1386-1388
[5] Vanderpump MP, et. al. Epidemiology and prevention of clinical and subclinical hypothyroidism. *Thyroid.* 2002;12:839-847
[6] Davis PJ, et al. Hypothyroidism in the elderly. *Compr Ther.*1984;10:17-23
[7] Bailes BK, et al. Hypothyroidism in elderly patients. *AORN J.* 1999;69:1026-30

Thyroid function tests in patients in myxedema coma are consistent with severe overt hypothyroidism, in which TSH is >10 mIU/L and circulating T3 and T4 levels are well below the normal reference ranges. Other laboratory abnormalities seen in patients in myxedema coma include anemia, elevated creatinine kinase (CK), elevated creatinine, elevated liver transaminases, hypercapnia, hyperlipidemia, hypoglycemia, hyponatremia, hypoxia, leukopenia, and respiratory acidosis.

Intravenous levothyroxine is considered first-line treatment for myxedema coma[8]. The ATA guidelines recommend a loading dose of 200-400 mcg of levothyroxine IV in most patients, and a lower loading dose for smaller patients, older patients, or patients with cardiac disease. The loading dose should be followed by a daily replacement dose of 1.6 mcg/kg of IV levothyroxine, followed by oral levothyroxine therapy once there is sufficient clinical improvement for the patient to take medications by mouth.

Given conversion of T4 to T3 may be decreased in patients with myxedema coma, co-administration of liothyronine may be considered[9]. If intravenous liothyronine is used, ATA guidelines recommend a loading dose of 5-20 mcg followed by a maintenance dose of 2.5-10 mcg every 8 hours, with a caveat that patients who are small in size, older, or with cardiac conditions should be treated with lower doses.

The goals of therapy are to achieve an improvement in mental status, cardiac function, pulmonary function and metabolic parameters, and to prevent death. Serum thyroid hormone (T3 and T4) levels may improve or normalize within days of initiating treatment. In comparison, improvement in TSH levels is typically gradual and normalization may take weeks. An increase in levothyroxine dose, with or without the addition of liothyronine therapy, may be considered in patients who do not exhibit an improvement in T3 and T4 levels or a reduction in TSH levels.

In conclusion, myxedema coma is a serious condition, characterized by a state of severely decompensated hypothyroidism, which if untreated can be life-threatening.

2.1. Analysis of Current Treatment Options

FDA-approved therapies for myxedema coma include intravenous levothyroxine and liothyronine. Refer to Table 1 for a list of currently available products approved to treat myxedema coma. Levothyroxine therapy is generally well tolerated. Adverse events (AE) typically occur due to over-treatment and are consistent with signs and symptoms of hyperthyroidism, e.g., tachycardia, palpitations, increased blood pressure, nervousness, diarrhea, abdominal cramps, hyperthermia, heat intolerance, weight loss, increased appetite, and tremors.

[8] Jonklaas, J et. al. Guidelines for the Treatment of Hypothyroidism. *Thyroid*. 2014; 24:1670-1751
[9] Kwaku MP, et al. Myxedema Coma. *Journal of Intensive Care Medicine*. 2007; 22:224

Table 1: FDA-approved therapies for myxedema coma

Product (s) Name (Application number/Company)	Dosage forms and strengths available	Year of Approval	Approved dosing	Clinical studies conducted
Approved levothyroxine therapies				
Levothyroxine sodium (NDA 202231 – Fresenius Kabi USA)	Lyophilized powder for injection in single dose vials: 100 mcg and 500 mcg	2011	An initial intravenous loading dose between 300 to 500 mcg, followed by once daily intravenous maintenance doses between 50 and 100 mcg, until the patient can tolerate oral therapy.	None
Levothyroxine sodium (ANDA 206163 – Piramal Critical)	Lyophilized powder for injection in single dose vials: 100 mcg and 500 mcg	2016	Same as above.	None
Levothyroxine sodium (ANDA 208749 – Maia Pharmaceuticals, Inc.)	Lyophilized powder for injection in single dose vials: 100 mcg, 200 mcg and 500 mcg	2018	Same as above.	None
Levothyroxine sodium (NDA 210632 – Fresenius Kabi USA)	Solution, available in a concentration of 20 mcg/mL, 40 mcg/mL and 100 mcg/mL	2019	Same as above.	None
Levothyroxine sodium (ANDA 208837 – Dr. Reddy's Labs LTD)	Lyophilized powder for injection in single dose vials: 100 mcg	2020	Same as above.	None
Approved liothyronine therapies				
Triostat (NDA 020105 – Par Pharmaceuticals, Inc.)	Solution available in a concentration of 10 mcg/ml	1991	An initial intravenous loading dose between 25 to 50 mcg. In patients with cardiovascular disease, a loading dose of 10 to 20 mcg is recommended. Both initial dose and subsequent dose should be determined on the basis of continuous monitoring of patient's clinical condition and response to Triostat therapy, with 4 to 12 hours between doses.	None
Liothyronine sodium (ANDA 076923 – X-Gen Pharmaceuticals,	Solution available in a concentration of 10 mcg/ml	2005	Same as above.	None

Product (s) Name (Application number/Company)	Dosage forms and strengths available	Year of Approval	Approved dosing	Clinical studies conducted
Inc.)				

NDA = New Drug Application
ANDA = Abbreviated New Drug Application
Source: Approved labels at: drugs@FDA and https://dailymed.nlm.nih.gov

In conclusion, the current armamentarium of products approved in the US to treat myxedema coma includes multiple levothyroxine sodium injectable drugs. However, the majority of these are available as a lyophilized powder for injection that require reconstitution prior to administration. This introduces a risk for medical errors and a potential for contamination. Currently, there is one injectable formulation that is available as a ready-to-use premixed solution (NDA 21063, approved 2019, Fresenius Kabi). The levothyroxine sodium injectable formulation proposed under NDA 214253 will provide another treatment option for myxedema coma that will be available as a ready-to-use premixed solution.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Multiple formulations of oral and intravenous synthetic levothyroxine are currently marketed in the U.S. All of these products were approved via the 505(b)(2) pathway, relying on the safety and efficacy of a previously approved, bioequivalent LT4 product and/or on published literature. All available intravenous synthetic levothyroxine products were also approved via the 505(b)(2) pathway and relied on the safety and efficacy information from another, bioequivalent oral or IV LT4 product. The proposed product will be the first levothyroxine formulation administered intravenously from ready-to-use single-dose vials for the treatment of myxedema coma.

The Applicant submitted NDA 214253 for a ready-to-use 100 mcg/mL levothyroxine sodium solution in single-dose vials via the 505(b)(2) pathway, relying on the FDA's previous findings of safety and effectiveness for levothyroxine sodium for injection approved under NDA 202231. Currently, there is one injectable levothyroxine formulation that is available as a ready-to-use premixed solution in multi-dose vials (NDA 21063, approved 2019, Fresenius Kabi). The levothyroxine sodium injectable formulation proposed under NDA 214253 will provide another treatment option for myxedema coma that will be available as a ready-to-use premixed solution.

3.2. Summary of Presubmission/Submission Regulatory Activity

On December 12, 2018, the Agency provided written responses to the Applicant's pre-Investigational New Drug (pre-IND) meeting package. The Agency agreed that the NDA for

levothyroxine IV may be submitted via the 505(b)(2) pathway, provided the Sponsor establishes a bridge between their drug product and the listed drug (Levothyroxine Sodium for Injection, NDA 202231). The Agency agreed that clinical studies, including human bioavailability studies, would not be required. However, nonclinical studies assessing the safety of impurities that exceed International Conference on Harmonization (ICH) qualification thresholds and are not present in the listed drug may be required.

On February 27, 2019, the Applicant requested another pre-IND meeting seeking the Agency's agreement regarding topics covering pharmaceutical quality. Specifically, the Applicant proposed providing 6 months of accelerated and long-term stability testing data on 3 primary batches at the time of NDA submission. Additionally, the Applicant proposed an initial expiration period of (b) (4) months. On April 24, 2019, the Agency provided written responses in disagreement with the proposed plan. The Agency stated that a complete application with 12-month stability data would need to be submitted at the time of NDA submission, and the expiration date of the drug product would be reviewed during the NDA review cycle.

On January 30, 2020, a pre-NDA meeting was held between the Applicant and the Agency. The Agency stated that, because the formulation of the proposed drug product differed in component and composition from that of the listed drug product, the Applicant would need to provide additional evidence, which may come from published literature, that the differences in the inactive ingredients (e.g., SBECD and disodium edetate dihydrate) do not affect the pharmacokinetic (PK) performance or efficacy/safety of the drug product in order to support the bridge between the proposed and listed drug products and thereby justify a biowaiver under 21 CFR 320.22(b)(1).

On May 1, 2020, the Applicant submitted a request for a Type C guidance meeting to gain the Agency's approval on the proposed bridging study. On July 14, 2020, the Agency provided written responses, agreeing with the proposed strategy. The Agency also agreed that the information provided adequately established the safety of the excipients, and a need for additional nonclinical data to support the NDA was unlikely.

On July 17, 2020, the Applicant submitted NDA 214253 for levothyroxine sodium ready-to-use solution for the treatment of myxedema coma via the 505(b)(2) pathway, relying on the FDA's finding of safety and effectiveness of levothyroxine sodium for injection approved under NDA 202231.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No clinical studies were performed, and therefore no OSI audit was requested.

4.2. Product Quality

Product Quality Recommendation:
Overall, the product quality, including the drug substance, drug product, and facility manufacturing and testing compliance, are adequate and the recommendation is approval.

Product Overview:
The proposed product is a sterile, clear, colorless to yellow solution provided in a 1mL single dose vial for intravenous injection. Each mL of the product contains 100 µg of levothyroxine sodium dissolved in water for injection along with 80 mg betdex sulfobutyl ether sodium (also known as sulfobutyl ether beta-cyclodextrin sodium, SBECD), 50 mcg arginine, 50 mcg disodium edetate dihydrate (EDTA), and (b) (4) mg sodium chloride. The final pH of the formulation is adjusted with hydrochloric acid or sodium hydroxide to (b) (4).

Since the proposed product contains the same active ingredient in the same concentration as the listed drug, the applicant requested a biowaiver per 21 CFR 320.24(b)(6). The excipients present in the proposed product differ quantitatively and qualitatively (Q1/Q2) from the listed drug, thus the applicant provided additional information to bridge the proposed product to the listed drug and requested a waiver of in vivo bioavailability studies. This waiver request was granted by the biopharmaceutics reviewer.

Drug Substance:
The drug substance, levothyroxine sodium, is manufactured by (b) (4) (b) (4) The molecular weight of Levothyroxine sodium is 798.9g/mol on an anhydrous basis. The molecular formula of levothyroxine sodium hydrate is C15H10I4NaO4. X H2O.

The Applicant referenced Type II DMF (b) (4) for all chemistry, manufacturing and control (CMC) information for the drug substance. The CMC reviewer determined that, based on the information provided in DMF (b) (4), the proposed drug substance specifications meet all requirements of the current USP monograph for levothyroxine sodium, with the addition of appearance, residual solvents, bioburden and endotoxin. The limits for organic impurities and related substances conform to the limits listed in the USP monograph. Based on available stability data, a retest date of (b) (4) months is granted for levothyroxine sodium drug substance when stored at (b) (4) (b) (4)

The CMC reviewer concluded that the CMC information in the DMF and the proposed drug substance specification acceptance criteria are acceptable.

Drug Product:
The drug product is a preservative free product packaged in a single dose vial.

Drug Product Formulation: The proposed drug product, levothyroxine sodium injection 100 mcg/mL, is a clear, colorless to slightly yellow, sterile, aqueous solution packaged in a 2 mL (b) (4) clear glass vial and sealed with a 13mm (b) (4) (b) (4) stopper and a flip-off seal. The finished product is packaged in cartons. Each vial contains 1 mL of the drug product. Each mL of the drug product solution contains 100 mcg of levothyroxine sodium, 80 mg of SBECD, 50 mcg arginine, 50 mcg EDTA, (b) (4) mg sodium chloride, and water for injection. The final pH of the formulation is adjusted with hydrochloric acid or sodium hydroxide to (b) (4).

The proposed excipients have previously been used in approved parenteral products and their levels in the drug product are well below the levels listed in FDA's inactive ingredient database. SBECD is included in the proposed product for (b) (4) (b) (4) Sodium chloride is provided for tonicity adjustment. Arginine is provided for the (b) (4) EDTA is provided for (b) (4) (b) (4)

The product is light sensitive and is stored in a carton in order to prevent exposure to light during shelf-life. The container closure components proposed for use in the product are known for use in approved products and the applicant provided a leachables study assessment to assure the safety of the proposed container closure system.

Dr. Dhanalakshmi Kasi, the Office of Pharmaceuticals Quality (OPQ) reviewer, reviewed the drug product information, including drug product composition, drug product specification, excipient information, analytical methods, container closure system, compatibility information including glass delamination study data, photostability and stability data. The compatibility of the active ingredient with excipients and the container closure components is supported by drug product stability data.

The drug product is tested for visual appearance, identity, particulate matter, pH, osmolality, assay, purity and impurities, extractable volume, uniformity of dosage units, closure integrity, EDTA content, endotoxin content, and sterility. Dr. Kasi's review concluded that the proposed specifications are adequate to support the quality of the proposed product.

Manufacturing Process and Controls:

The manufacturing process involves [redacted]

The Applicant is using the following in-process quality control tests: [redacted] The composition of the drug product, the drug product manufacturing process, batch size, and the packaging system used in stability studies are the same as those proposed for commercial use. The process reviewer concluded that the proposed drug product manufacturing process controls are adequate.

Microbiological controls:
The microbiological controls used in the drug product manufacturing process [redacted] were determined to be adequate by the Microbiology reviewer. The [redacted] and validation information provided in Type V DMFs [redacted] were also determined to be adequate.

Control Strategy:
The critical quality attributes of the product are controlled through [redacted] The CMC review team determined that the proposed control strategy is assure the quality of the product.

Based on available stability data, OPQ granted an expiration period of 24 months when stored

at 25°C (77°F) in the commercial packaging protected away from light. Any unused portion should be discarded.

Facility compliance information:
Facility compliance information for the drug product and drug substance manufacturing and testing facilities was reviewed by the Office of Process Manufacturing Assessment (OPMA) reviewer, who concluded that the facilities associated with the application are adequate. Thus, the overall manufacturing inspection recommendation (OMIR) from OPMA is approve.

4.3. Clinical Microbiology

Clinical Microbiology Recommendation:
The applicant's justification for a biowaiver is adequate and additional in vivo bioequivalence (BE) bridging studies are not needed to support approval. The overall recommendation is to grant the biowaiver request and to approve the product.

Request for Biowaiver
The proposed product, levothyroxine sodium injection, is a solution dosage form and is quantitatively and qualitatively (Q1/Q2) different from the listed drug, a lyophilized powder that requires reconstitution before use. The proposed product formulation uses SBECD (b) (4), sodium chloride for tonicity adjustment, arginine for (b) (4) and EDTA (b) (4) The pH of the proposed product is approximately (b) (4) pH units (b) (4) than the listed drug (pH (b) (4) (b) (4)). To bridge the proposed product to the LD product, the Applicant requested a biowaiver of in vivo bioavailability studies under 21 CFR 320.24(b)(6) on the basis that changes to the listed drug formulation will not affect the pharmacokinetic profile of levothyroxine sodium injection.

To support a biowaiver, the applicant provided a physicochemical properties comparison between the proposed drug product and the listed drug product after reconstitution in 0.9% sodium chloride solution. The applicant provided adequate justification that the change in formulation and pH will not affect the pharmacokinetic performance or clinical safety and efficacy outcomes of the proposed drug product when compared to the reference product. The Biopharmaceutics reviewer deemed the applicant's justification for a biowaiver to be adequate and concluded that additional in vivo bioequivalence (BE) bridging studies are not needed.

4.4. Devices and Companion Diagnostic Issues

This is neither a device nor a companion diagnostic.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The nonclinical program is supportive of marketing approval; no deficiencies were identified in the pharmacology/toxicology information. Custopharm, Inc. did not conduct animal studies in support of the marketing application for Levothyroxine Sodium for Injection, as there were no issues identified with the levothyroxine drug substance that would require toxicological testing. Rather, the Applicant seeks to rely on published literature and FDA's previous findings of safety and effectiveness for levothyroxine sodium for injection, using levothyroxine sodium for injection marketed by Fresenius Kabi under NDA 202231, as the listed drug.

The proposed drug product formulation contains a profile of impurities consistent with ICH thresholds and inactive ingredients similar to the listed drug, except for the inclusion of sulfobutyl ether beta-cyclodextrin sodium (SBECD). SBECD is (b) (4) included in the formulation at a concentration of 80 mg/mL. The maximum daily amount of SBECD a patient would be exposed to is below the maximum daily limit present in other FDA-approved therapies and is additionally supported by published nonclinical toxicology studies conducted with SBECD.

The Applicant conducted leachable tests using the drug formulation in primary packaging (vials and stoppers) for levothyroxine sodium injection after storage at 40ºC for 6 months and 25ºC for 10 months. A toxicological assessment of seven organic leachable compounds detected above the analytical threshold indicates that leachables may be present in levothyroxine sodium injection with calculated permissible daily exposures providing ≥21-fold multiples to the estimated maximum daily exposure.

No deficiencies were noted in the nonclinical program. No issues were identified in the safety assessment for the components of the drug formulation or for the leachable profile from the container-closure system.

5.2. Referenced NDAs, BLAs, DMFs

NDA 202231 Levothyroxine Sodium for Injection.

5.3. Pharmacology

Levothyroxine sodium for injection is intended to act like the endogenous T_4 produced naturally in the human thyroid gland. T_4 is converted to T_3, the active metabolite, in the liver and kidney. The solubility of T_3 and T_4 is increased by attaching to thyroid hormone binding proteins, which transport and bind to thyroid hormone receptors in the cytoplasm and nucleus. Therefore, levothyroxine sodium acts as a replacement of natural T_4, alleviating the symptoms of T_4 deficiency. The pharmacologic profile of levothyroxine (T4) sodium is well established. This drug product is a synthetic T4.

5.4. ADME/PK

The absorption, distribution, metabolism, excretion and pharmacokinetics (ADME/PK) of Levothyroxine Sodium for Injection was cross-referenced to NDA 202231.

Table 2. Data referenced from NDA 202231 nonclinical review.

Type of Study	Major Findings
Absorption	
	T_{max} 3-7 hours for tablet and solution oral formulations Half-life approximately 8.6 to 14.6 hours in dogs
Distribution	
	Minimal placental transfer of T_4 occurred in rats during last days of gestation.
Metabolism	
	Sodium salicylate increased the rate of T_4 disappearance from the blood and increased the uptake of T_4 in a model of isolated perfused rat livers, as well as increased rates of conjugation of T_4 with glucuronic acid.
Excretion	
	Hepatobiliary clearance of T_4 mediated by hepatic microsomal enzyme induction. Approximately 3% of total administration dose of T_4 was excreted into bile in rats.

5.5. Toxicology

No animal toxicology, genotoxicity, carcinogenicity or reproductive toxicology studies were conducted with this injectable levothyroxine product, as there were no identifiable issues with the drug substance that would necessitate or be further informed by animal testing.

5.5.1. Safety Assessment of Sulfobutyl ether beta-cyclodextrin sodium, NF (SBECD)

Levothyroxine Sodium Injection, 100 µg/mL is supplied as a sterile solution in 1 mL vials for intravenous administration. Each vial contains levothyroxine sodium USP, L-arginine USP, edetate disodium USP, sulfobutyl ether beta-cyclodextrin sodium NF, sodium chloride USP, negligible amounts of sodium hydroxide NF or hydrochloric acid NF as needed, and water for injection USP. The proposed drug product formulation contains SBECD (b) (4) at a concentration of 80 mg/mL, which differs from that of the listed drug product.

The Applicant has proposed a loading dosing of 300 to 500 µg (3 to 5 mL), followed by a once daily maintenance dose between 50 and 100 µg (0.5 to 1 mL). Under this dosing regimen, a patient may receive up to 400 mg SBECD in a loading dose followed by up to 80 mg/day during the maintenance treatment. SBECD content in FDA-approved therapies varies from

approximately 200 mg to 3200 mg with maximum daily dosing limits up to 9600 mg (see Table 3). Therefore, the proposed concentration of SBECD in the Applicant's Levothyroxine Sodium Injection of 80 mg/mL, with exposure between approximately 80 mg from a maintenance dose to 400 mg as a loading dose, falls within the daily intake of previously approved therapies.

SBECD has been tested in chronic, reproductive, and genetic toxicology studies in animals.[10] Evidence of vacuolation of renal proximal tubule epithelium and foamy (lipid-laden) macrophages in the lung have been observed in rats and dogs. The NOAEL for renal effects was defined at 80 mg/kg and 30 mg/kg in rats and dogs, respectively. The NOAEL for the presence of macrophages in lung was defined at 160 mg/kg and 200 mg/kg in rats and dogs, respectively. Doses of up to 1500 mg/kg in dogs have been reported with no clinical evidence of toxicity. Levothyroxine Sodium Injection proposed doses up to 500 µg delivering 400 mg SBECD to a 60 kg patient provides a 2.5- and 16.7-fold safety margin with respect to the NOAEL of renal and lung findings in the dog.

Table 1: Comparison of Content of Sulfobutyl ether beta-cyclodextrin sodium in FDA-Approved Therapies

Approved Therapy	Drug Product Presentation	MRHD	Total Volume used for MRHD (mL)	SBECD Concentration (mg/mL)	SBECD Maximum Daily Limit (mg)
Levothyroxine sodium	100 mcg/1 mL	500 mg	5	80	400
Amiodarone HCl Injection IV	50 mg/mL	Load: 150 mg Follow: 0.5 to 1 mg	3	225	675
Aripiprazole Injection IM	9.75 mg/1.3 mL	30 mg/day	4	199.5	798
Delafloxacin Injection IV	300 mg powder	300 mg BID	NA	2400	4800
Voriconazole	200 mg powder	200-300 mg BID	NA	3200	9600
Ziprasidone Injection IM	20 mg/mL	40 mg/day	2	294	588

5.5.1. Toxicological Assessment of Levothyroxine Sodium Injection Leachables

The applicant used inverted storage of the drug formulation in primary packaging (vials and stoppers) for levothyroxine sodium injection at 40ºC for 6 months and 25ºC for 10 months. Seven organic leachable compounds were detected using HS-GC-FID/MS analysis for volatile

[10] Luke DR et al. Review of the Basic and Clinical Pharmacology of Sulfobutylether-b-Cyclodextrin (SBECD). *Journal of Pharmaceutical Sciences*. 2010; 99:3291–3301.

compounds, GC-FID/MS analysis for semi-volatile compounds, and LC-DAD/MS analysis for non-volatile compounds and reported per ICH Q3D guidelines for parenterally dosed drug products. ICP-MS analysis was used to detect inorganic compounds. The analytical evaluation threshold (AET) was calculated at (b) (4) µg/vial and the analytical threshold (AT) set at (b) (4) µg/mL as injected into the instrument. The limit of quantitation (LOQ) was similar to the AT. All organic leachable compounds above the AET compared to the negative control were reported.

The threshold of toxicological concern (TTC) was defined for the recommended doses of levothyroxine sodium injection at 5 µg/day, allowing for data collection at 1.5 µg/day TTC as a worst-case scenario (FDA-ICH M7(R1), 2018).

Maximum daily exposures (MDEs) were calculated based on the LOQ with the following equations:

$$MDE\ (\mu g/day) = \left(\frac{LOQ\ (\mu g/mL) \times Fill\ volume\ (mL)}{Concentration\ Factor \times Vials\ extracted}\right) \times (Vials/day) \times \left(\frac{1}{Uncertainty\ Factor}\right)$$

Where

$$1.5\ \mu g/day = \left(\frac{\text{(b) (4)}\ \mu g/mL \times 1\ mL}{3 \times 1\ vial}\right) \times (5\ vials/day) \times \left(\frac{1}{\text{(b) (4)}}\right)$$

The resulting MDEs for the seven leachables ranged from (b) (4) µg/day, see Table 4.

A toxicological assessment for the seven organic leachables was conducted based on literature obtained from different sources (PubMed, FDA, National Toxicology Program-NTP, EPA, European Food Safety Agency-EFSA, OECD, Hazardous Substance Data Bank-HSDB, Cosmetic Ingredient Review-CIR, FAO/World Health Organization Expert Committee on Food Additives-JECFA, the International Agency for Research on Cancer-IARC, and the European Chemicals Agency-ECHA). Route-to-route modifying factors were incorporated into safe level calculations and animal toxicology data was used if available. The "read-across" approach uses surrogates and/or chemical classes with known toxicity data in cases where adequate compound-specific toxicity data are unavailable. This approach was used selecting compounds with similarity in structure to the leachable, physio-chemical profile, likely toxicity, pharmacokinetics, and the availability of toxicity data.

The permissible daily exposures (PDE) were calculated following ICH Q3C(R7) formula for solvents (ICH 2019). The formula was:

$$\text{Safe Dose or PDE (mg/day)} = \frac{\text{NOEL x Weight Adjustment}}{\text{F1 x F2 x F3 x F4 x F5}}$$

Table 2: Identified Leachable Compounds from Custopharm Drug Container Closure System

(b) (4)

The no observed effect level (NOEL, or lowest observed effect level [LOEL] in the absence of a NOEL) for a particular study was adjusted for human body weight and the factors in the denominator are modifying factors defined in the table below:

Table 3: Modifying Factors

Modifying Factors		Range
F1	Extrapolation between species	1-12
F2	Variability between individuals	10
F3	Extrapolation of study duration	1-10
F4	To account for severe toxicity (non-genotoxic carcinogenicity, neurotoxicity or teratogenicity)	1-10
F5	To account for use of low observable effect level	10
Additional		1-10

Additional modifying factors (typically 10) were used to account for different exposure routes.

The Applicant noted that the ICH PDE methodology followed for the toxicological assessment of leachables was not specifically developed for leachable compounds, but it provides a conservative estimate of a safe human exposure level. The reviewer agreed with the proposed methodology as it is the current acceptable methodology by the Agency (Safety Evaluation of Impurity & Extractable/Leachables Workshop, FDA-CDER-OND, 2019).

A summary of calculated MDEs, PDEs (values confirmed by reviewer), available chronic safe injection levels, and estimated exposure multiples is presented in Table 5. The PDE or chronic safe injection levels are (b) (4) than the calculated MDEs for the leachables potentially present in Custopharm's levothyroxine sodium injection, providing an acceptable margin of safety to the MDE for each leachable.

Table 4: Summary of Calculated MDEs and PDEs for Levothyroxine Sodium Injection Leachables

(b) (4)

(b) (4)

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted a 505(b)(2) NDA for Levothyroxine Sodium Injection, 100 mcg/1 mL solution, referencing NDA 202231, which is Levothyroxine Sodium for Injection, a lyophilized powder formulation to be used after reconstitution with 5 mL of 0.9 % Sodium Chloride Injection, USP.

The Applicant submitted a formal waiver request for *in vivo* bioavailability/bioequivalence (BA/BE) studies per 21 CFR 320.24(b)(6), indicating that the bioequivalence of the proposed product is considered self-evident. While there was no new clinical study conducted with the proposed levothyroxine sodium injection, the impact of the inactive ingredient betadex sulfobutyl ether sodium (SBECD), on the bioavailability of levothyroxine was needed as this inactive ingredient is not in the listed drug product.

The Applicant concluded that the impact of SBECD on levothyroxine pharmacokinetics (PK) was not significant based on in vitro protein binding study results and information from literature.

The Applicant's conclusion that SBECD has an insignificant impact on levothyroxine PK is acceptable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

The sponsor provided scientific rationale that there was no significant impact of SBECD on levothyroxine pharmacokinetics based on the following:

- SBECD does not affect the in vitro protein bindings of levothyroxine, indicating that there is no significant change in levothyroxine distribution by SBECD compared to excipients of the listed drug product.
- SBECD systemic exposure following administration of the proposed product is lower than other approved products containing SBECD.

The Applicant's rationale is acceptable from a clinical pharmacology perspective.

6.2.1. General Dosing and Therapeutic Individualization

General Dosing

An initial intravenous loading dose of Levothyroxine Sodium for Injection between 300 to 500 mcg, followed by once daily intravenous maintenance doses between 50 and 100 mcg, should be administered, as clinically indicated, until the patient can tolerate oral therapy. The proposed dosing is consistent with the dosing for other intravenously administered synthetic levothyroxine products approved for treatment of myxedema coma.

Therapeutic Individualization

Starting and maintenance dosing for intravenous levothyroxine should be adjusted based on the patient's age, general physical condition, cardiac risk factors, clinical severity of myxedema, and duration of myxedema symptoms.

Lower starting doses are recommended for elderly patients and patients with underlying cardiovascular disease.

Outstanding Issues

The Applicant addressed the potential impact of SBECD on the PK of levothyroxine as advised by the Agency. There are no outstanding issues from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

To support the biowaiver request, the Applicant conducted the following studies as communicated previously (See further details of communication related to the biowaiver and bridging in meeting minutes in DARRTS dated 2/5/2020):

- in vitro protein binding of levothyroxine in the presence of SBECD
- literature data review for the systemic SBECD exposure following clinically relevant dosing of the proposed product, referring to the known maximum tolerable dose and toxicity threshold of SBECD
- literature data review related to the impact of renal function on SBECD exposure as a worst-case situation of SBECD exposure increase and its potential effect on levothyroxine PK

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

6.3.2. Clinical Pharmacology Questions

Is there any potential impact of SBECD on levothyroxine distribution?

Results of the in vitro protein binding study indicate that the potential impact of SBECD on levothyroxine distribution is limited.

The Applicant determined the ratios of protein binding of levothyroxine to plasma and components of human plasma, which are known to bind to levothyroxine, based on a standard protein binding method using ultrafiltration method and LC/MS/MS bioanalytical method for levothyroxine concentration measurement (Table 6). To evaluate the impact of SBECD on levothyroxine protein binding, the ratios were compared between the proposed product and listed drug product (Table 6).

There was no significant difference in levothyroxine binding to plasma or components of human plasma with the proposed product compared to that of listed drug product (Table 6). The levothyroxine concentrations used in the protein binding study covered levothyroxine concentrations at clinically-relevant IV doses in literature: approximately average 10 mcg/dL following 428 mcg IV with a typical radioimmunoassay for levothyroxine or Cmax < 250 ng/mL following oral 600 mcg with LC/MS assay. Overall, the study design and results support that there is no significant impact of SBECD on levothyroxine PK, and the conclusions are acceptable from a clinical pharmacology perspective.

Table 5: Summary of protein binding of levothyroxine to human plasma and components of human plasma

Levothyroxine Concentration	Source	Percent Binding			
		Plasma	Human Serum Albumin	Thyroxine Binding Globulin	Human Prealbumin
50.0 ng/mL	(b) (4) (levothyroxine reference standard)	99.992%	99.367%	99.984%	99.826%
	Custopharm product	99.994%	98.680%*	99.969%	99.756%
	LD product	99.996%	99.397%	99.972%	99.813%
250 ng/mL	(b) (4) (levothyroxine reference standard)	99.985%	99.613%	95.358%	99.830%
	Custopharm product	99.982%	96.434%	97.070%	98.883%
	LD product	99.985%	99.643%	97.128%	99.858%

* an estimate with re-assay as concentration of the post-ultrafiltration sample was above the quantifiable limit of 500 pg/mL

(Source; Table 6, Module 5.3.5.4, m5-dp-levo-biobridge.pdf, CTD)

Is there any potential impact of SBECD on levothyroxine disposition?

There is no literature information that directly addresses the potential impact of SBECD on levothyroxine disposition following IV administration. Therefore, literature data were reviewed based on potential worst-case scenarios, including:

- if there is any situation that SBECD exposure is increased in a clinical scenario, and
- if the increased SBECD can affect exposure of drugs.

SBECD is known to be eliminated by renal excretion from the body following IV administration of a drug. This indicates that the SBECD exposure increases in renal impairment and corresponding exposure change of drug(s) can be considered as an example of a worst-case scenario.

Using literature, the Applicant concluded that the estimated in vivo SBECD levels following administration of the proposed product (SBECD 400 mg or 80 mg per day with dosing of 500 mcg or 100 mcg levothyroxine injection, respectively) were significantly lower than levels of clinical concern as follows:

- 11.3-fold less than the NOAEL from nonclinical studies
- 22.7-fold less than the reversible toxicities that were observed in nonclinical studies
- 59.9-fold less than that of other approved drug (i.e., Baxdela, delafloxacin IV injection, where up to 4800 mg of SBECD may be administered)

Literature[11] indicates there is an increase in SBECD exposure with worsening degrees of renal impairment; 1.2-, 2.1- and 5.2-fold SBECD AUC increase in mild, moderate, and severe renal impairment sub-groups, respectively, compared to that of normal. It appears that the significant SBECD exposure increase was not associated with the exposure change of drug (i.e., delafloxacin); approximately 2-fold increase following IV (formulation with SBECD) vs. 1.5-fold increase following oral (formulation without SBECD) in severe renal impairment.[11]

Overall, literature information, including labeling of approved products with SBECD and publications, indicate that the amount of SBECD with the proposed product is below that of other approved products with SBECD, and its exposure is significantly below the threshold level for toxicities. Further, the increase in SBECD exposure in a worst-case situation (such as renal impaired patients) may not significantly impact the levothyroxine exposure considering that the disposition mechanisms between the two compounds are not overlapping, as SBECD is mainly eliminated through renal excretion and levothyroxine is eliminated by sequential deiodination in the liver.

7 Sources of Clinical Data and Review Strategy

No clinical studies were submitted under this NDA.

8 Statistical and Clinical and Evaluation

[11]Hoover RK et al. Clinical Pharmacokinetics of sulfobutylether-beta-cyclodextrin in patients with varying degree of renal impairment. J Clin Pharmacol, 58:814-822.

No clinical studies were submitted under this NDA.

9 Advisory Committee Meeting and Other External Consultations

There is no Advisory Committee meeting for this application.

10 Pediatrics

This application does not trigger PREA because the proposed product is not for a new indication, new dosage form, new dosing regimen, or new route of administration, nor does it contain new active ingredients.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Final labeling negotiations were ongoing at the time of completion of this review. Minor labeling changes between the proposed product and the listed drug were made in order make the proposed product's label consistent with the most recently updated levothyroxine product label.

12 Risk Evaluation and Mitigation Strategies (REMS)

No Risk Evaluation and Mitigation Strategies are recommended for this product.

13 Postmarketing Requirements and Commitment

None.

14 Appendices

14.1. Financial Disclosure

Not applicable. No clinical studies were submitted under this NDA.

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/s/

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