CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210632Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY MEMORANDUM

NDA	210632
Submission Date	15 June 2018
Brand Name	N/A
Generic Name	Levothyroxine Sodium Injection
Reviewer	Suryanarayana Sista, Ph.D.
Team Leader	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	DMEP
Sponsor	Fresenius Kabi LLC
Formulation; Strength	Solution for injection at three strengths in single dose clear glass vials: • 100 µg/5 mL (20 µg/mL) • 200 µg/5 mL (40 µg/mL) • 500 µg/5 mL (100 µg/mL)
Indication	Treatment of myxedema coma

The Sponsor submitted a New Drug Application in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act to seek marketing clearance for Levothyroxine Sodium Injection. The Reference Listed Drug (RLD), Levothyroxine Sodium for Injection is also manufactured by the Sponsor. No clinical studies were conducted in support of this NDA, the Sponsor relied completely on literature references. A summary of clinical pharmacology of levothyroxine sodium was prepared based on information from 6 peer-reviewed publications and 2 text books.

- This application also contains a request for the waiver of in vivo bioavailability / bioequivalence studies. In addition, a request for waiver of pediatric studies was also provided.

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 210632's Clinical Pharmacology data and finds it acceptable.
Post Marketing Requirement or Post Marketing Commitment
None.

Background:

Levothyroxine Sodium injection, for intravenous use was initially approved for marketing on 24 June 2011 (NDA 202231). The formulation approved for NDA 202231 was lyophilized Levothyroxine Sodium that had to be reconstituted for injection by aseptically adding 5 mL of 0.9% Sodium Chloride Injection, USP to the lyophilized powder. The current NDA submission (NDA 210632) will supply Levothyroxine Sodium Injection in single dose vials containing (a) 100 mcg per 5 mL (20 mcg per mL), (b) 200 mcg per 5 mL (40 mcg per mL), and (c) 500 mcg per 5 mL (100 mcg per mL). In support of this application, the sponsor provided various literature references.

The referenced citations that the Sponsor submitted are the same as that submitted for NDA 202231. The literature citations supporting the Clinical Pharmacology section of this NDA were reviewed by Dr. S.W. Johnny Lau (see DARRTS, reference ID: 2946952, also https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202231Orig1s000ClinPharm.pdf). Bioanalytical methods to quantitate levothyroxine and clinical pharmacology of levothyroxine are also discussed in these literature citations.

For a complete discussion of the Clinical Pharmacology information of levothyroxine pertaining to the current NDA submission, which includes literature cited, the reader is referred to Dr. Lau's review of NDA 202231, since no new additional clinical pharmacology related information was added to the current submission.

Labeling Comments

The following are the labeling recommendations relevant to the clinical pharmacology sections for NDA (b) (4). The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

7 DRUG INTERACTIONS

7.1 Drugs Known to Affect Thyroid Hormone Pharmacokinetics

Many drugs affect thyroid hormone pharmacokinetics and metabolism (e.g., synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to Levothyroxine Sodium Injection (see Tables 1-3). (b) (4)

Table 1: Drugs That May Alter T_4 and Triiodothyronine (T_3) Serum Transport Without Effecting Free Thyroxine (FT_4) Concentration (Euthyroidism)

Drug or Drug Class	Effect
Clofibrate Estrogen-containing oral contraceptives Estrogens (oral) Heroin / Methadone 5-Fluorouracil Mitotane Tamoxifen	These drugs may increase serum thyroxine-binding globulin (TBG) concentration.
Androgens / Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid	These drugs may decrease serum TBG concentration.

Potential impact (below): Administration of these agents with levothyroxine results in an initial transient increase in FT_4. Continued administration results in a decrease in serum T_4 and normal FT_4 and TSH concentrations.	
Salicylates (> 2 g/day)	Salicylates inhibit binding of T_4 and T_3 to TBG and transthyretin. An initial increase in serum FT_4 is followed by return of FT_4 to normal levels with sustained therapeutic serum salicylate concentrations, although total T_4 levels may decrease by as much as 30%.
Other drugs: Carbamazepine Furosemide (> 80 mg IV) Heparin Hydantoins Non-Steroidal Anti-inflammatory Drugs - Fenamates	These drugs may cause protein-binding site displacement. Furosemide has been shown to inhibit the protein binding of T4 to TBG and albumin, causing an increase free T4 fraction in serum. Furosemide competes for T4-binding sites on TBG, prealbumin, and albumin, so that a single high dose can acutely lower the total T4 level. Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total and free T4 may be reduced by 20% to 40%, but most patients have normal serum TSH levels and are clinically euthyroid. Closely monitor thyroid hormone parameters.

Table 2: Drugs That May Alter Hepatic Metabolism of T_4 (Hypothyroidism)

Potential impact: Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased levothyroxine requirements.	
Drug or Drug Class	**Effect**
Phenobarbital Rifampin	Phenobarbital has been shown to reduce the response to thyroxine. Phenobarbital increases L-thyroxine metabolism by inducing uridine 5'-diphospho-glucuronosyltransferase (UGT) and leads to a lower T4 serum levels. Changes in thyroid status may occur if barbiturates are added or withdrawn from patients being treated for hypothyroidism. Rifampin has been shown to accelerate the metabolism of levothyroxine.

Table 3: Drugs That May Decrease Conversion of T_4 to T_3

Potential impact: Administration of these enzyme inhibitors decreases the peripheral conversion of T_4 to T_3, leading to decreased T_3 levels. However, serum T_4 levels are usually normal but may occasionally be slightly increased.	
Drug or Drug Class	**Effect**
Beta-adrenergic antagonists (e.g., Propranolol > 160 mg/day)	In patients treated with large doses of propranolol (> 160 mg/day), T_3 and T_4 levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. It should be noted that actions of particular beta-adrenergic antagonists may be impaired when the hypothyroid patient is converted to the euthyroid state.
Glucocorticoids (e.g., Dexamethasone > 4 mg/day)	Short-term administration of large doses of glucocorticoids may decrease serum T_3 concentrations by 30% with minimal change in serum T_4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T_3 and T_4 levels due to decreased TBG production (See above).
Other drugs: Amiodarone	Amiodarone inhibits peripheral conversion of levothyroxine (T4) to triiodothyronine (T3) and may cause isolated biochemical changes (increase in serum free-T4, and decreased or normal free-T3) in clinically euthyroid patients.

7.2~~1~~ Antidiabetic Therapy

Addition of levothyroxine to antidiabetic or insulin therapy may result in increased antidiabetic agent or insulin requirements. Careful monitoring of (b) (4) glycemic control is recommended (b) (4).

7.3~~2~~ Oral Anticoagulants

Levothyroxine increases the response to oral anticoagulant therapy. Therefore, a decrease in the dose of anticoagulant may be warranted with correction of the hypothyroid state (b) (4).

[redacted] to permit appropriate and timely dosage adjustments.

7.43 Digitalis Glycosides

Levothyroxine may reduce t~~T~~he therapeutic effects of digitalis glycosides [redacted]. Serum digitalis glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides.

7.54 Antidepressant Therapy

Concurrent use of tricyclic (e.g., amitriptyline) or tetracyclic (e.g., maprotiline) antidepressants and levothyroxine may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac arrhythmias and central nervous system [redacted] stimulation [redacted] Levothyroxine may accelerate the onset of action of tricyclics. Administration of sertraline in patients stabilized on levothyroxine may result in increased levothyroxine requirements.

7.65 Ketamine

Concurrent use of ketamine and levothyroxine may produce marked hypertension and tachycardia.~~;~~ Closely monitor blood pressure and heart rate in these patients. [redacted]

7.76 Sympathomimetics

Concurrent use of sympathomimetics and levothyroxine may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.

7.87 Drug-Laboratory Test Interactions

Consider changes in TBG concentration when interpreting T4 and T3 values. Measure and evaluate unbound (free) hormone and/or determine the free T4 index (FT4I) in this circumstance. [redacted] Pregnancy, infectious hepatitis, estrogens, estrogen containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. Nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, androgens, and corticosteroids decrease TBG concentration. [redacted] Familial hyper or hypo thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9,000.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Thyroid hormones exert their physiologic actions through control of DNA transcription and protein synthesis. Triiodothyronine (T3) and levothyroxine (T4) diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins.

The physiological actions of thyroid hormones are produced predominantly by T3, the majority of which (approximately 80%) is derived from T4 by deiodination in peripheral tissues.

12.2 Pharmacodynamics

Levothyroxine sodium is a synthetic T4 hormone that exerts the same physiologic effect as endogenous T4, thereby maintaining normal T4 levels when a deficiency is present. [redacted]

[redacted]

12.3 Pharmacokinetics

[redacted]

Distribution

Circulating thyroid hormones are greater than 99% bound to plasma proteins, including thyroxine binding globulin (TBG), thyroxine binding prealbumin (TBPA), and albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for T4 partially explains the higher serum levels, slower metabolic clearance, and longer half life of T4 compared to T3. Protein bound thyroid hormones exist in reverse equilibrium with small amounts of free hormone. Only unbound hormone is metabolically active. Many drugs and physiologic conditions affect the binding of thyroid hormones to serum proteins *[~~see~~ [redacted] Drug Interactions (7)].* Thyroid hormones do not readily cross the placental barrier *[see [redacted] Use in Specific Populations (8.1)].*

Metabolism

T4 is slowly eliminated. The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately eighty percent of circulating T3 is derived from peripheral T4 by monodeiodination. The liver is the major site of degradation for both T4 and T3, with T4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T4 is deiodinated to yield equal amounts of T3 and reverse T3 (rT3). T3 and rT3 are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

[redacted] *Excretion*

Thyroid hormones are primarily eliminated by the kidneys. A portion of the conjugated hormone reaches the colon unchanged, where it is hydrolyzed and eliminated in feces as the free hormones. Urinary excretion of T4 decreases with age.

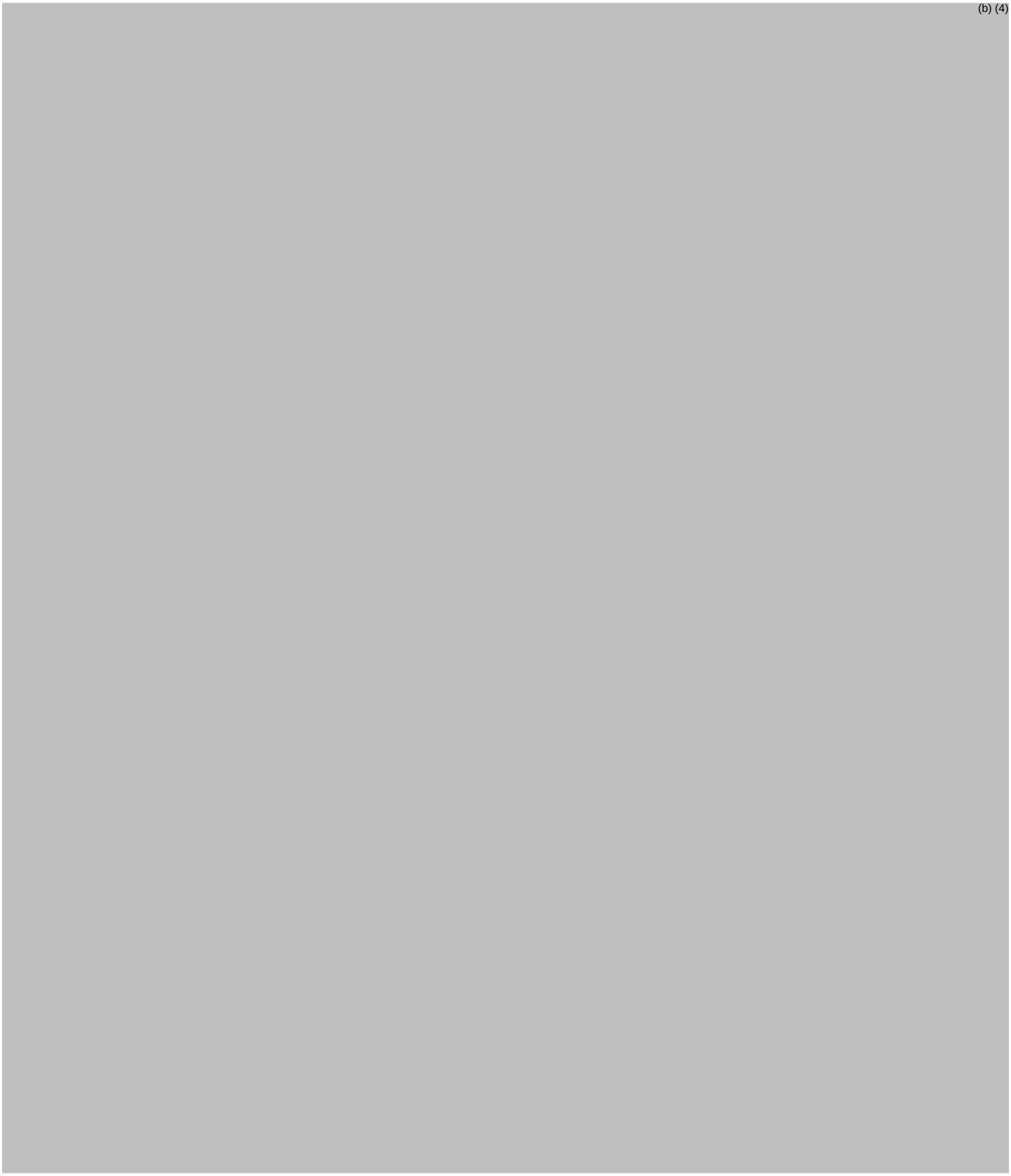
Table 1: Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

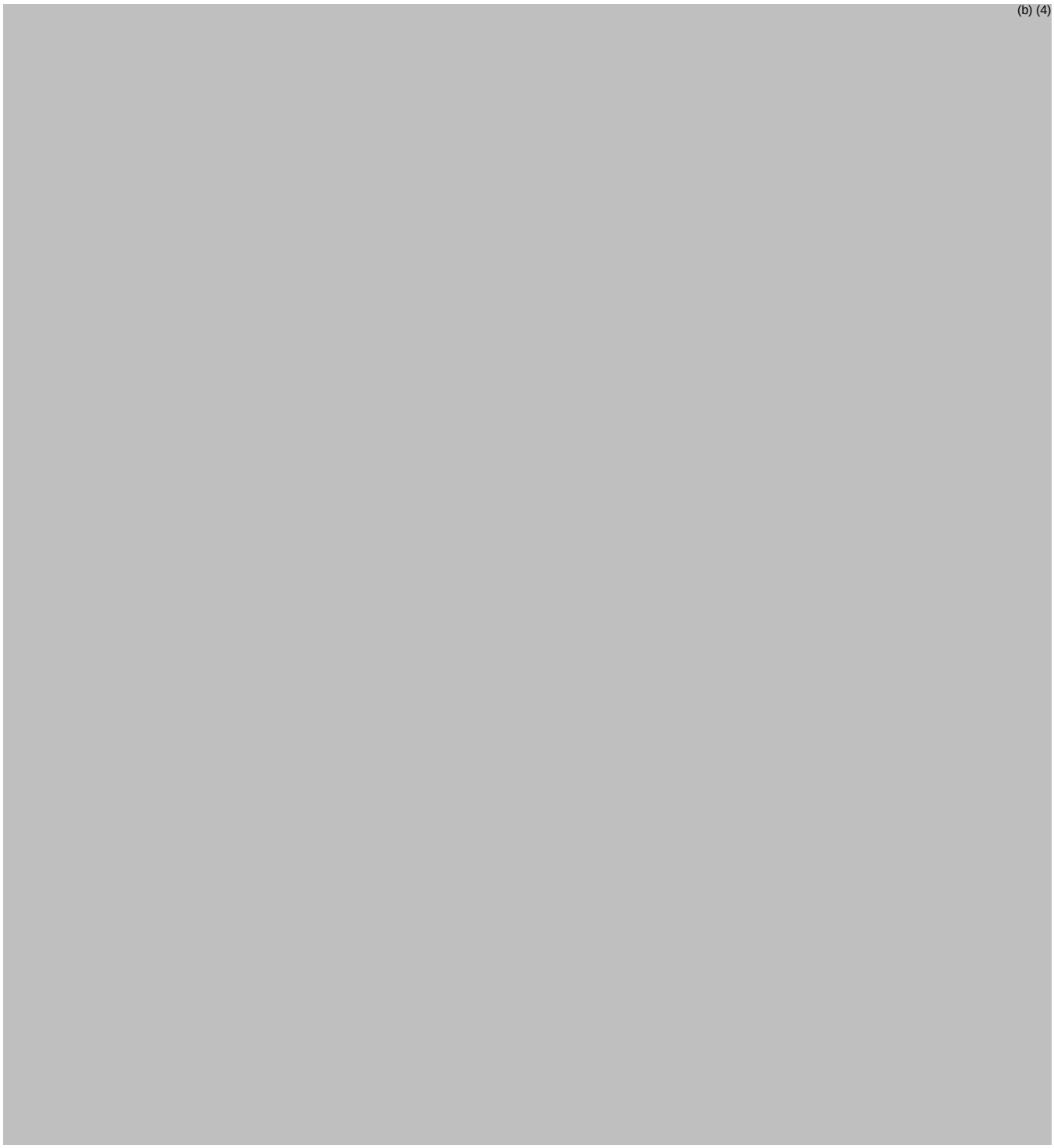
Hormone	Ratio in Thyroglobulin	Biologic Potency	Half-Life (Days)	Protein Binding (%)[2]
T_4	10 to 20	1	6 to 8[1]	99.96

T_3	1	4	≤ 2	99.5

T_4: Levothyroxine
T_3: Liothyronine
[1] 3 to 4 days in hyperthyroidism, 9 to 10 days in hypothyroidism.
[2] Includes TBG, TBPA, and TBA.

(b) (4)

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/s/

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