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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name Levothyroxine sodium for injection
(Proposed) Trade Name Levothyroxine sodium for injection
Therapeutic Class Thyroid hormone
Applicant APP Pharmaceuticals, LLC

Formulation(s) Injection
Dosing Regimen Initial loading dose of 300-500 µg IV followed by daily maintenance doses of 50-100 mcg until oral therapy is tolerated
Indication(s) Treatment of myxedema coma
Intended Population(s) Adults

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1 Recommendations/Risk Benefit Assessment

Levothyroxine Sodium for Injection (IV levothyroxine) is a marketed, unapproved drug now proposed for the treatment of "myxedema coma, (b) (4)

(b) (4) In order to comply with the Agency requirement of submitting a New Drug Application (NDA) in order to obtain FDA approval², the Sponsor now submits a 505(b)(2) application relying solely on medical literature. The proposed dosage is an initial loading dose between 300 to 500 µg followed by daily maintenance doses between 50 and 100 µg until the patient can tolerate oral therapy.

Levothyroxine is approved as an oral formulation under many trade names and available as a generic drug. Oral levothyroxine products are indicated for the treatment of hypothyroidism and pituitary TSH suppression, but the label for these products state that, because of unpredictable absorption of levothyroxine from the gastrointestinal tract in a severely hypothyroid state, oral thyroid hormone drug products are not recommended to treat myxedema coma. In this respect, IV levothyroxine is considered a bridge, a temporary treatment, until oral therapy can be initiated.

There are currently no intravenous levothyroxine formulations approved in the US.

1.1 Recommendation on Regulatory Action

I recommend approval of Levothyroxine sodium for injection for the treatment of myxedema coma. (b) (4)

(b) (4) The following recommendations, however, apply to this approval:

- At the time this Review was written, labeling negotiations have not commenced with the Sponsor. This Reviewer's suggested revisions are included at the end of this Document.
- Because the Sponsor did not conduct a bioavailability study for this product, the Division recommends language in the label alerting providers to this lack of data when transitioning patients from IV levothyroxine to an oral product. Conversely, the Division recommends caution when switching patients from oral to IV levothyroxine.

¹ From Sponsor's proposed label, submitted with NDA August 31, 2010

² FDA Warning Letter issued by FDA Chicago District on December 18, 2006

1.2 Risk Benefit Assessment

Although oral levothyroxine is available for the treatment of hypothyroidism, it is not indicated for the treatment of myxedema coma, since in this condition rapidly-acting treatment that avoids the need for gastrointestinal absorption is required.

The Sponsor submitted literature to support the safety and efficacy of IV levothyroxine. This includes 45 clinical efficacy studies and 34 efficacy/safety studies. The Sponsor has not performed any clinical trials.

Efficacy

Because of the rarity of the condition as well as the acceptance of intravenous levothyroxine as the standard of care for the condition, conducting a randomized clinical trial for patients with myxedema coma is impractical if not impossible. However, the literature submitted in this application supports the efficacy of IV levothyroxine for the treatment of patients with myxedema coma. The first series of myxedematous patients treated with IV levothyroxine was reported in 1964.¹ The articles submitted in this application—which included case reports, case series, meta-analyses, and reviews—collectively confirm the efficacy and necessity of IV levothyroxine for the treatment of patients with myxedema coma.

Safety

The safety profile of oral levothyroxine products is well-characterized and generally applies to the intravenous formulation. The Sponsor submitted literature to characterize the safety profile of IV levothyroxine. Specifically, IV levothyroxine is associated with cardiac toxicity, including arrhythmia and myocardial infarction, for high doses and in the elderly and in those with underlying cardiac disease. Cautious use of IV levothyroxine, including not exceeding the recommended dose and careful monitoring in at-risk populations, can limit these adverse events.

Proposed dose

For the indication of myxedema coma, the Sponsor proposes an initial loading dose of 300 to 500 µg followed by daily maintenance doses between 50 to 100 µg, until the patient can tolerate oral therapy. Based on the literature, this Reviewer agrees with the recommended dose ranges.

The Sponsor has provided limited bioavailability data to aid in the transition from IV to oral levothyroxine therapy. A more detailed discussion of this is under Clinical Pharmacology.

Limitations

A prominent limitation in this application was the complete reliance on literature. However, the literature was sufficient to support the efficacy and safety of IV levothyroxine. The literature was not sufficient to provide important bioavailability data,

leading to cautionary language in the label, discussed under Efficacy and Labeling Recommendations.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable to this Application.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable to this Application.

2 Introduction and Regulatory Background

The Agency informed the Sponsor in 1996 that Levothyroxine Sodium for Injection is categorized as a “Marketed Unapproved Drug”. This followed the publication of the FDA Guidance entitled “Marketed Unapproved Drugs—Compliance Policy Guide”ⁱⁱ.

The Sponsor met with the Division on March 18, 2008 to discuss their intention of submitting a 505(b)(2) NDA for levothyroxine sodium for injection.

2.1 Product Information

Levothyroxine sodium for injection contains synthetic crystalline levothyroxine sodium. The drug product is a sterile, lyophilized powder to be reconstituted in saline. It is available in 3 different strengths (100 µg /vial, 200 µg /vial, and 500 µg /vial) in single-use vials.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently no approved intravenous (IV) formulations of levothyroxine.

2.3 Availability of Proposed Active Ingredient in the United States

IV levothyroxine is currently marketed in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

Not applicable to this application.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A Pre-IND/NDA meeting between the Division and the Sponsor was held on March 18, 2008. Key discussion and points of agreement included:

- Given the wide variety of dosing recommendations in the literature, the Sponsor would need to propose and justify an appropriate dosing regimen for the treatment of myxedema coma.
- Because the proposed IV formulation serves as a bridge during acute illness, knowledge of relative bioavailability is important. Therefore a single-dose crossover pharmacokinetic study, comparing the proposed to-be-marketed IV levothyroxine to a marketed oral levothyroxine tablet, was recommended by the Division.

In a post-meeting decision conveyed to the Sponsor, the Division recommended that regarding bioavailability data, the Sponsor should consider conducting a single IV pharmacokinetic (PK) study with their product or providing the data based on literature. The literature data the Sponsor submitted with the meeting background package was *not* sufficient to characterize the PK of IV levothyroxine.

2.6 Other Relevant Background Information

In the clinical spectrum of hypothyroidism, myxedema coma is the most extreme form. Because of the difficulty in promptly recognizing and treating affected patients, the diagnosis carries a high mortality. Thought to be rare today, there are approximately 300 cases reported in the literature.ⁱⁱⁱ Since hypothyroidism in general is more common in women and in the elderly, it is believed that most patients who present with myxedema coma are elderly women. In a patient who presents with signs and symptoms of hypothyroidism with mental status changes, the diagnosis depends on a determination of thyroid-stimulating hormone (TSH). Once the diagnosis is made, therapy should be instituted immediately. Even so, the mortality rate approaches 50% to 60%.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the submission quality is adequate. Because of the nature of this application, the Sponsor, in prior agreement with the Division, did not submit Integrated Summaries for either safety or efficacy. Rather, the literature upon which was the Application is based is presented in a Summary of Clinical Efficacy and a Summary of Clinical Safety.

3.2 Compliance with Good Clinical Practices

Not applicable to this application.

3.3 Financial Disclosures

Not applicable to this application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to Dr. Leginus' Review for full details. There are no major approvability issues.

4.2 Clinical Microbiology

Refer to Dr. Mello's Review for details. There are no approvability issues.

4.3 Preclinical Pharmacology/Toxicology

Refer to Dr. Tsai-Turton's Review for full details. There are no approvability issues.

4.4 Clinical Pharmacology

Refer to Dr. Johnny Lau's Review for full details. Information in this Section is extracted from his Review.

4.4.1 Mechanism of Action

Levothyroxine sodium for injection is identical to endogenous levothyroxine. Both thyroid hormone, thyroxine (T3) and triiodothyronine (T4) have important effects on development, growth, and metabolism.^{iv}

4.4.2 Pharmacodynamics

There is a consistent exposure-response relationship, with a decrease in TSH upon repeated dosing of levothyroxine.

4.4.3 Pharmacokinetics

Once administered, the synthetic levothyroxine is indistinguishable from endogenous levothyroxine. More than 99% of thyroid hormone is bound by plasma proteins, but only the unbound hormone is metabolically active. The binding of thyroid hormone to serum proteins is affected by many drugs and physiologic conditions.

Elimination of levothyroxine is slow with a half-life of 6 to 8 days. The major site of levothyroxine degradation is the liver, where it is deiodinated to liothyronine. Thyroid hormone primarily undergoes renal excretion with some fecal elimination.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The literature submitted by the Sponsor is summarized in Tables under Efficacy and Safety, below.

5.2 Review Strategy

The articles submitted in support of both safety and efficacy of IV levothyroxine were individually reviewed. Articles discussing oral levothyroxine alone or the use of

triiodothyronine (T3) alone were not reviewed in detail, as they were not directly pertinent to this application. The vast majority of submitted literature pertained to the treatment of myxedema coma, and therefore the emphasis of the literature review was placed on this indication. The Sponsor submitted few articles relevant to the use of IV levothyroxine in non-myxedema coma patients.

In addition, findings from this Reviewer's own literature search are referenced periodically in this document and overall were consistent with data derived from the Sponsor's submitted literature.

5.3 Discussion of Individual Studies/Clinical Trials

There were no Sponsor-conducted studies or trials performed to support this application. All data submitted is derived from literature, discussed under Efficacy and Safety below.

6 Review of Efficacy

Efficacy Summary

The Sponsor's support for efficacy of IV levothyroxine is based on 45 articles from the literature. These include case series, reviews, and trials primarily discussing the treatment of myxedema coma. Twelve of the 45 discuss the use of either oral levothyroxine or T3 (oral or IV) and therefore are not subject to a detailed discussion in this Review. For each paper submitted, the table below details the type of literature, the number of subjects studies (for case series and trials), and pertinent efficacy results. Papers considered pivotal for this discussion are discussed in greater detail following the table.

The data, including collective observations, recommendations, and anecdotal experience, support the efficacy of IV levothyroxine for the treatment of myxedema coma. The observations and recommendations derived from the literature yield a range of recommended doses pertaining to the treatment of myxedema coma.

With the exception of the administration of excessive doses of IV T4 (defined by this Reviewer as exceeding 500 µg IV), most studies show that IV T4 therapy is effective in doses up to 500 µg daily. A number of Authors discussed below, including Jordan, Bagdade, Mazzaferri, Smallridge, Olsen, Wall, and Fliers, all agree that treatment of myxedema coma should be initiated with an IV bolus of between 300 and 500 µg. Although there are some who recommend an initial IV bolus of less than 300 µg, no Author recommends a dose exceeding above 500 µg. Given the fairly narrow spectrum of opinions and conclusions, a range of 300-500 µg as an initial IV dose appears

effective and allows for the practice of the art of medicine. With this recommendation, the clinician can then decide if a patient requires and can tolerate a dose on the lower or higher end of the proposed recommended range.

Maintenance dosing, daily doses that follow the initial IV bolus, is discussed less frequently in the published literature. Among the Authors who did discuss it, there appears to be agreement that daily maintenance doses of 50-100 µg are effective, until oral doses can be tolerated.

Since IV levothyroxine is intended as a temporary treatment, it would be important for a clinician to know how to transition a patient to oral therapy. However, because a bioavailability study was not performed, this information can only be construed from the literature, which also offers limited data using unapproved levothyroxine formulations. Two older studies demonstrate that absorption of the oral dose varies from 48-74% of the intravenous dose.^{vi} Differences in absorption primarily account for the wide range of values, and a clinician would need to cautiously use this data on a case-by-case basis, combined with repeated measurements of thyroid function and clinical assessments.

Therefore, although such bioavailability data would be useful, it is not critical for the following reasons:

- In clinical practice, a general idea of the conversion from IV to oral, based on limited literature, is understood.
- In general, when initiating oral levothyroxine, it is standard of care to reassess a patient clinically and with laboratory data at a minimum of 6 weeks after the drug is started. Therefore, unless a patient did not follow-up with their clinician, it would be unlikely that a patient would remain at a suboptimal dose for an extended period of time.

6.1 Indication

The Sponsor proposes levothyroxine for injection “for treatment of myxedema coma,

(b) (4)

The use of levothyroxine for injection for the treatment of myxedema coma is the primary subject of discussion in this Review.

The medical literature does not recognize (b) (4) and therefore this Review does not discuss it further.

(b) (4)

(b) (4)
Myxedema coma is the end stage of untreated or inadequately treated hypothyroidism and the physical findings are not specific.^{vii} (b) (4)

(b) (4)

Importantly, the Sponsor is not seeking an indication for treating patients on chronic oral levothyroxine therapy who require temporary IV levothyroxine, a use that is likely more common than myxedema coma. The Sponsor did not conduct a bioavailability study to yield data that is important when converting a patient from oral to IV levothyroxine.

6.1.1 Methods

All literature in support of efficacy is included in Table 1. Literature included in the table encompasses observational studies, case studies, and reviews. Because of the limitations associated with studying a rare disease such as myxedema coma, this body of summarized literature serves to collectively support the efficacy of levothyroxine for injection.

Following Table 1 is a more in-depth discussion of articles which this Reviewer considers particularly vital in this application that is wholly reliant in literature. Because of the unusual nature of this application, including a lack of results from a dedicated clinical trial, template sections are omitted when non-applicable.

In general, the case series and meta-analyses submitted utilized similar tools in assessing efficacy. These included measurements of thyroid function tests and clinical assessments, such as vital signs, level of consciousness, and ultimately survival, to assess efficacy of the designated treatment.

6.1.2 Demographics

The Sponsor summarized demographic data for the published articles that contained original clinical data related to the use of IV levothyroxine. Not all articles reported patient age and/or sex. For patients with myxedema coma, the age range of treated subjects was 20-90 years. However, the subjects were predominantly elderly women. In the Sponsor's database, there was only one treated patient under the age of 30 years, a 20 year old man with typhoid fever (Rodriguez, 2004).

Table 1 Clinical Efficacy Studies Reported in the Literature

Author	Indication studied	Literature category	Products used/discussed	No. of subjects	Primary endpoints	Efficacy Results/Recommendations on Dosing
Rawson, 1953 ^{viii}	Myxedema coma	Case Series	T4 3 mg IV versus T3 1 mg IV	1	BMR, UA, Stool analysis, serum cholesterol	Both products produced similar endpoints. However, T3 exerted a quick, short-lived effect, whereas L-thyroxine had a slow, prolonged effect.
Holvey, 1964 ^{ix}	Myxedema coma	Case Series	T4 120-500 µg IV	7	Improved vital signs, return to consciousness	All patients had improvements of VS in 6-12 hours. All patients returned to consciousness in 24-36 hours.
Green, 1968 ^x	Myxedema coma	Guidelines	T3 and T4 IV	n/a	Clinical outcome	Initial IV doses for full replacement should be either T4 500 µg OR T3 120 µg.
Rosenberg, 1968 ^{xi}	Myxedema coma	Review	T4 500 µg IV followed by daily doses of T4 50-75 µg IV.	n/a	Physical examination, laboratory findings, x-rays	Early treatment should be initiated with either IV T4 or enteral T3 (because of risk of arrhythmia associated with IV T3).
Senior, 1971 ^{xii}	Myxedema coma	Case Series and Discussion	T4 100 µg TID IM	1	Clinical outcome	Patient became alert within 3 days. MC should be treated with 400-500 µg T4 IV plus hydrocortisone. T3 is associated with a more variable therapeutic response as well as cardiac toxicity.
Blum, 1972 ^{xiii}	Myxedema coma	Review	Less than 500 µg IV T4 as initial dose or T3 10-25 µg IV given 8-12 hours.	n/a	Clinical outcome	Author primarily recommends 500 µg of L-thyroxine intravenously as initial dose. Another option is T3 IV, 10 to 25 µg given every 8-12 hours.
Ridgeway, 1972 ^{xiv}	Primary hypothyroidism	Open-label trial	2 groups: 1) 428 µg T4 IV followed by 100 µg daily for 9 days 2) 750 µg T4 IV followed by 200 µg daily for 9 days	14 total (7 per group)	Laboratory values	TSH levels decreased in both groups within 24 hours, but were more rapidly decreased in Group #2. All subjects reportedly tolerated the large doses well.
Klein, 1973 ^{xv}	Myxedema coma	Letter to the Editor (response to	T4 IV, T3 IV	NA	Clinical endpoints	The Author questions the use of high doses of IV thyroid hormone as well as the lack of complications noted.

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Author	Indication studied	Literature category	Products used/discussed	No. of subjects	Primary endpoints	Efficacy Results/Recommendations on Dosing
		Ridgeway 1972)				Ridgeway responds that in the young as well as healthy old, large doses are likely warranted.
Menendez, 1973 ^{xvi}	Myxedema coma	Review	T4 IV, T3 IV	NA	Clinical outcomes	The Author states therapy is either T3 given by NG tube or IV T4. In an emergency, large doses should be given: 400-500 µg T4 in a single dose followed by 50 µg IV or 0.1 mg orally daily. Also, T3 has been used in doses of 12.5 µg q6h given via NG tube. <u>Oral and intramuscular absorption is uncertain initially.</u> T4 is favored because it has a less arrhythmic effect.
Nicoloff, 1976 ^{xvii}	Myxedema coma	Review	T4 IV	NA	Clinical outcome	Initially, because of sluggish circulatory and GI concerns, all medications in MC should be administered the IV route. High doses of thyroid hormone are recommended. Administration of 500 µg IV T4 to an average-sized adult will restore circulating thyroxine level to about half the euthyroid value. IV T4 does not require a repeat dose for at least one week after initial administration. Its therapeutic margin of safety is much wider than that of T3. There are no significant adverse metabolic effects if a treated patient is subsequently found to not have hypothyroidism. IV T4 produces definitive improvement in clinical status within 6-36 hours. <u>Its use has shifted clinical outcomes from 80% mortality before the 1960s to approximately 80% survival.</u>
Jordan, 1983 ^{xviii}	Myxedema coma	Review	Initial dose:	n/a	Clinical outcomes	The Author's recommendation, based on

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Author	Indication studied	Literature category	Products used/discussed	No. of subjects	Primary endpoints	Efficacy Results/Recommendations on Dosing
			T4 400 µg IV Maintenance dose: T4 50 µg			Ridgeway's recommendations, is for an initial IV dose of 400 µg followed by 50 µg daily.
Hylander, 1985 ^{xxix}	Myxedema coma	Meta-analysis	T3 (oral and IV), T4 (oral and IV), or a combination	11	Mortality, estimated levels of T3 and T4	In this retrospective study, only 4/11 patients survived. Excessive use of T3 was associated with a higher mortality rate.
Bagdade, 1986 ^{xx}	Myxedema coma	Guidelines	T4 300 µg IV	n/a	Clinical outcomes	Patients should be given an initial dose of T4 300 µg IV followed by maintenance doses of 50-200 µg IV until PO administration is possible.
Mazzaferri, 1986 ^{xxi}	Myxedema coma	Symposium	Initial dose: T4 300 µg IV by slow infusion over first day Subsequent doses: T4 50 µg IV daily until consciousness is regained	n/a	Clinical outcomes	Risk factors for mortality in MC are hypotension and other serious underlying conditions.
Mitchell, 1989 ^{xxii}	Myxedema coma	Review	T3 T4	n/a	Clinical outcomes	Recommendations are an initial T4 IV dose of 300-500 µg as a bolus or slow infusion followed by 50-100 µg /day.
Arlot, 1991 ^{xxiii}	Myxedema coma	Observational	2 groups : 1) T4 IV 1000 µg IV, or 2) 500 µg oral T4 followed by 100 µg PO daily	7 (2 in Group 1 and 5 in Group 2)	Laboratory values, clinical improvement	A clinical response is seen within 36 hours, even when using oral T4. Two patients, one in each group, died of myocardial infarction.
Gavin, 1991 ^{xxiv}	Myxedema coma	Review	Initial dose : T4 IV 500 µg IV Maintenance dose: T4 IV 50-100 µg	n/a	Laboratory values	Indications of recovery with initial dose are rising body temperature and heart rate and should appear within 8-12 hours. Serum TSH decreases over 24 to 48 hours.

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Author	Indication studied	Literature category	Products used/discussed	No. of subjects	Primary endpoints	Efficacy Results/Recommendations on Dosing
			daily			
Smallridge, 1992 ^{xxv}	Myxedema coma	Review	Initial dose: T4 IV 200-300 µg Maintenance dose: 50-100 IV µg/day	n/a	Laboratory values	An unnecessary dose (due to an initial incorrect diagnosis) likely causes no harm. The author claims that some experts' recommendations for an initial loading dose of 500 µg IV were made prior to the recognition of euthyroid sick syndrome, and that perhaps some of the treated subjects were not actually hypothyroid. Also, the mortality rate is higher for treated subjects with a higher post-treatment T3 level. The author recommends lower doses until more definitive data are established.
Tsitouras, 1995 ^{xxvi}	Myxedema coma	Review	n/a	n/a	n/a	The author states that 1000 µg IV of T4 is excessive and predisposes to cardiac risks. A more acceptable regimen is 300-400 µg IV with daily IV maintenance doses until oral therapy is possible.
Jordan, 1995 ^{xxvii}	Myxedema coma	Review	Initial dose: T4 IV 300-500 µg followed by 50 µg IV daily until the patient can take oral medication.	n/a	n/a	Some combine T4 with T3. Doses of T3 exceeding 76 µg are associated with a fatal outcome.
Olsen, 1995 ^{xxviii}	Myxedema coma	Case series and review	T4 IV	1	Survival	The patient survived. The Author recommends 250-500 µg T4 IV, followed by maintenance therapy.
Yamamoto, 1999 ^{xxix}	Myxedema coma	Case series and meta-analysis	T4 IV	8	Mortality	Although high-doses replacement has been recommended for treatment of myxedema coma, the author found that high-dose treatment (IV T4 ≥ 500 µg /d) were significantly associated with a fatal outcome within 1 month of treatment. The author advocated treating elderly

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Author	Indication studied	Literature category	Products used/discussed	No. of subjects	Primary endpoints	Efficacy Results/Recommendations on Dosing
						patients with low-dose replacement.
Wall, 2000 ^{xxx}	Myxedema coma	Review	n/a	n/a	n/a	Most authorities recommend the use of T4 alone. Initial dose should be 100-500 µg IV followed by 75-100 µg IV daily until oral replacement is possible. The lower end of doses should be administered to patients who are frail or have other comorbidities, particularly cardiovascular disease.
Nagoaka, 2002 ^{xxxii}	Refractory hypothyroidism (single case)	Case series	Various oral and IV doses	1	Laboratory values	This is the first report of post-operative hypothyroidism that required 10 times the normal maintenance dose. Symptoms only resolved with daily IV administration of levothyroxine (150 µg daily).
Fliers, 2003 ^{xxxii}	Myxedema coma	Review	n/a	n/a	n/a	The most widely accepted recommendation is 300-500 µg IV T4, followed by 50 to 100 µg of IV T4 until oral medication can be given. Higher doses are associated with mortality. Combination therapy remains experimental. If no clinical improvement is seen after IV T4 treatment, T3 might be given.
Rodriguez, 2004 ^{xxxiii}	Myxedema coma	Review	High-dose: T4 500 µg IV Low-dose: no initial 500 µg IV bolus	High-dose: 6 Low-dose: 5	Mortality rate	Subjects treated with high-dose (300-500 µg T4 IV followed by 50-100 µg daily) fared better than those receiving low-dose.
Wartofsky, 2006 ^{xxxiv}	Myxedema coma	Review	Combination therapy	n/a	n/a	The author recommends therapy with T4 and T3. He advocates for an initial bolus of T4 200-250 µg IV, followed by 100 µg 24 hours later and then 50 µg daily as IV or PO, as tolerated. The initial dose of T3 is 10 µg given every 8-12 hours until the patient can take oral T4.

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Author	Indication studied	Literature category	Products used/discussed	No. of subjects	Primary endpoints	Efficacy Results/Recommendations on Dosing
Kwaku, 2007 ^{xxxv}	Myxedema coma	Review	T4 IV	n/a	n/a	Authors recommend T4 IV 200-300 µg IV, followed by 100 µg daily until bowel motility is adequate.

Adapted from Sponsor's NDA submission, Table 2.7.3-1

The specific articles discussed below are included in Table 1. While all literature in the Table contributes to the determination of efficacy, the articles below are highlighted and are discussed in greater depth since this Reviewer considers them particularly key to the Application. The articles include widely-referenced and respected papers with pivotal discussions of the treatment regimen and dosing of myxedema coma.

Papers discussing general treatment of myxedema coma

Holvey 1964

The Author describes 7 patients with myxedema coma, all who survived following IV boluses of T4, ranging in doses from 120-500 µg (average dose 411 µg). Following the bolus, these seven patients' had improvement in vital signs within 6-12 hours and a return to consciousness within 24-36 hours. He writes that "in contrast to triiodothyronine, the long half life of thyroxine obviates the need of administration of multiple doses." He also concludes that, based on calculations of the estimated depletion in the extrathyroidal hormone pool and the diminished fractional turnover rate, the deficiency can be corrected with 500 µg of levothyroxine. The Author emphasizes that oral therapy should be avoided because of the risks of poor absorption and pulmonary aspiration. Given the risk of cardiovascular complications, the question of whether replacement in myxedema coma should be initiated slowly or rapidly remains unanswered. Monotherapy with T4 is the treatment of choice on "pragmatic and physiological" grounds: long duration of action and predictable effect. T3, on the other hand, requires repeat dosing and is more likely to induce cardiovascular complications.

While Holvey does not emphasize the need for repeat dosing, the majority of more recent literature does include that recommendation.

Nicoloff 1976

The Author's recommendation for the treatment of myxedema coma is 500 µg of IV levothyroxine to the average size adult or 300 µg/m², as this restores circulating thyroxine levels to approximately half the euthyroid value. Serum triiodothyronine levels are also rapidly restored to a similar degree. The Author's reasons for the recommendation include:

- 1) The survival rate of treatment with intravenous thyroxine has been as successful as with any other form of administering thyroid hormone.
- 2) No repetitive dose of thyroid medication is required for at least 1 week after the initial administration, since the peak metabolic effect occurs at 10-12 days
- 3) The therapeutic margin of safety is greater with T4 than T3.
- 4) No significant metabolic effects will occur in a patient subsequently found not to have hypothyroidism.

Nicoloff also states that T3 may be used. While he states that T3 "may invite cardiovascular catastrophe", it may be advantageous in chronically ill patients, because there may be an impairment of conversion of T4 to T3 in this population.

Papers with specific discussion of dosing in myxedema coma

Although the articles above include discussion and recommendations of dosing, several submitted articles emphasized a discussion of proper dosing. These are mentioned here.

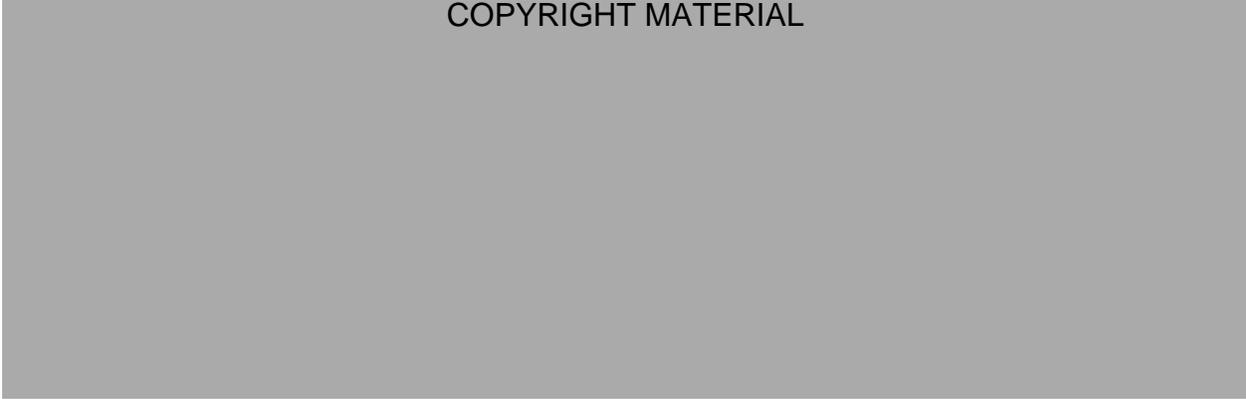
Blum 1972

The Author states that the goal of therapy is to replace the pool of depleted hormone. The dose of thyroxine required for this is based on calculations by Holvey et al and observations made by Ingbar et al and Sterling et al. In order to “replete an individual to a minimally euthyroid state with one dose of drug, 500 µg of L-thyroxine intravenously is recommended”. Some effect is noticed after 6 hours. The Author also writes that “it is reasonable to suppose that very rapid onset of L-triiodothyronine would evoke the most rapid return to a eumetabolic state. Generally 10 to 25 µg is given 8 to 12 hours intravenously.” The Author does not mention combination therapy (T4 plus T3).

Yamamoto et al 1999

In this case series, the Authors summarize the treatment of 8 patients with myxedema coma. The first 3 were treated with high-dose (75-150 µg T3 alone on Day 1) while the other 5 received a smaller amount of either T3 or T4. Individual doses are summarized in the table below.

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Two of the first 3 died of pneumonia and the other 5 recovered. In order to find factors associated with fatal outcome after treatment, the Authors searched the MEDLINE database. They found that greater age, cardiac complications, and high-dose thyroid replacement (LT4≥500 µg/day or LT3≥75 µg/day) were significantly associated with a fatal outcome within 1 month of treatment.

The Authors therefore recommend that elderly patients be treated with low-dose hormone replacement. A bolus of 500 µg T4 is tolerated by younger patients (<55 years) without cardiac complication.

Reviewer comment: Although there were clearly other differences among the 7 treated subjects, in this series, the 2 patients who received the highest doses of T3 died.

Rodriguez 2004

This was a prospective study was carried out to investigate the clinical and biochemical factors that are important in predicting the outcome of patients with myxedema coma. Eleven patients were treated over a period of 18 years. Patients were selected at random to be treated with two different regimens of LT4. Six received an initial dose of 500 µg IV followed by 100 µg IV daily until vital function were regained, free T4 was normalized and they were able to take oral medication. The other 5 patients were treated similarly but without the high-dose initial bolus. The results suggested that the patients treated with a high initial dose of T4 had a tendency toward better prognoses that those not treated with the initial dose.

7 Review of Safety

Safety Summary

The Sponsor's support for safety of IV levothyroxine is also derived from published literature reports. Forty studies were submitted, although not all specifically discussed IV levothyroxine. Accordingly, the focus in this Review is a discussion of safety findings in patients treated with IV levothyroxine. A number of articles already discussed under Efficacy are cited in this Section again as they pertain to a specific discussion of safety.

In many ways, the safety profile of IV levothyroxine is comparable to that of oral levothyroxine products and is therefore already established. On the other hand, the injection formulation, because of its rapid delivery into the bloodstream, is associated with cardiac morbidity and mortality, particularly when given in high bolus doses. Furthermore, this cardiac safety issue appears to be magnified in the likely patient population, since the majority of patients with myxedema coma are elderly with probable baseline cardiovascular disease.

The Sponsor also submitted safety data for the oral dosage forms of levothyroxine. These are not discussed in detail.

7.1 Methods

Specific sections of the template not applicable to the safety section of this 505(b)(2) application have been omitted.

All literature in support of safety is included in Table 3. Although many of the articles are identical to those presented under Efficacy, the discussion here relates to safety findings only.

Databases used to prepare the Sponsor's presentation of safety for IV and oral levothyroxine were as follows:

- APP Pharmaceutical's post marketing safety database for levothyroxine sodium for injection
- National Library of Medicine (NLM) MEDLINE/MEDLAR database using the terms "levothyroxine, thyroxine, or T4" and "myxedema coma, or myxedema, or myxedema"
- NLM's TOXLINE by using the terms "levothyroxine, thyroxine, or T4" and "myxedema coma, or myxedema, or myxedema"
- FDA Adverse Event Reporting System (AERS) database from 2008 to the present using the terms "levothyroxine, thyroxine, or T4" and "intravenous", or "levothyroxine, thyroxine, or T4" and "injection"
- Freedom of Information (FOI) summaries published on the world wide web
- Federal Register using terms "levothyroxine, thyroxine, or T4" and "intravenous", or "levothyroxine, thyroxine, or T4" and "injection"

Most studies that describe safety data related to the treatment of myxedema coma with the IV formulation of levothyroxine have clinical outcome, or mortality rate, as the primary safety outcome variable.

7.2 Adequacy of Safety Assessments

As all data was extracted from the literature, safety assessments were not consistent between articles. However, most of the articles reporting on patient treatment and monitoring included measures of thyroid function tests and clinical assessments.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A range of initial and maintenance IV doses were utilized among the literature submitted: initial doses of 120-1000 µg IV daily and maintenance doses of 50-150 µg daily until oral dose is tolerated.

7.3 Major Safety Results

The Table below lists some of the Sponsor-submitted literature to support the safety of IV levothyroxine. Although a number of the articles are also included in Table 1 above (efficacy), the focus in Table 3 is safety findings discussed in the literature. Following the table is further discussion of the most clinically important safety issues.

Table 3 Clinical Safety Studies Reported in the Literature

Author	Indication studied	Literature category	Products used/recommended	No. of subjects	Primary endpoints	Safety/Tolerability Results
Holvey, 1964	Myxedema coma	Case series	120-500 µg IV T4	7	1) improved vital signs 2) return to consciousness	1 patient experienced cerebral infarction following treatment
Rosenberg, 1968	Myxedema coma	Review	Levothyroxine 500 µg IV followed by daily doses of T4 50-75 µg IV.	n/a	Physical examination, laboratory findings, x-rays	Patients should be monitored for possible respiratory depression and complications from associated diseases.
Senior, 1971	Myxedema coma	CS and discussion	Levothyroxine sodium 100 µg TID IM	1	Clinical outcome	Cardiotoxicity observed with T3 is much greater than with T4.
Blum, 1972	Myxedema coma	Review	Less than 500 µg IV T4 as initial dose or T3 10-25 µg IV given 8-12 hours.	n/a	Clinical outcome	Caution if pressor amines are administered concomitantly. Concomitant administration of steroids is vital.
Ridgway, 1972	Non-comatose myxedema	Open-label	2 groups: 3) 428 µg levo followed by 100 µg daily for 9 days 4) 750 µg levo followed by 200 µg daily for 9 days	14 total (7 per group)	Laboratory values	ECG did not reveal any deterioration of T-wave morphology, ischemic changes, or ectopic beats.
Klein, 1973	Myxedema coma	Letter in Response to Ridgway, 1972	n/a	n/a	Clinical endpoints	The Author urges initiation of therapy with small doses to avoid ischemic myocardial effects.
Menendez, 1973	Myxedema coma	Review	n/a		Clinical outcome	IV administration of thyroid hormone avoids

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Author	Indication studied	Literature category	Products used/recommended	No. of subjects	Primary endpoints	Safety/Tolerability Results
						the use of a nasogastric tube with the attendant risk of pulmonary aspiration. Patients should be under cardiac monitoring during initial therapy.
Nicoloff, 1976	Myxedema coma	Review	IV Levothyroxine	n/a	Clinical outcome	High doses of IV levothyroxine may predispose to cardiovascular events.
Bacci, 1981 ^{xxxvi}	Myxedema coma	Case report	IV Levothyroxine 800 µg	1	Mortality	A 68 year old woman with myxedema became unresponsive 15 minutes after a high dose of IV Levothyroxine. She later died.
Mazzaferri, 1986	Hypothyroidism and Myxedema coma	Symposium	IV Levothyroxine 300 µg loading dose followed by IV Levo 50 µg daily	n/a	Clinical Outcomes	Large IV doses of thyroid hormone can precipitate cardiac arrhythmias and myocardial infarction, patients must be treated in an intensive care unit.
Jordan, 1983	Myxedema coma	Review	Levothyroxine 400 µg IV loading dose followed by 50 µg IV maintenance dose	n/a	TSH, T4, and T3	Levothyroxine therapy may result in cardiac ischemia and ventricular arrhythmias. Therefore patients should be monitored in an intensive care unit.
Mitchell, 1989	Myxedema coma	Review	Levothyroxine 300-500 µg IV followed by 50—100 µg daily thereafter.	n/a	Clinical outcomes	Administration of thyroid hormone in either form may precipitate myocardial ischemia and arrhythmias.

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Author	Indication studied	Literature category	Products used/recommended	No. of subjects	Primary endpoints	Safety/Tolerability Results
						Replacement should be done with careful monitoring.
Arlot, 1991 ^{xxxvii}	Myxedema coma	Observational	2 groups : 3) T4 IV 1000 µg IV, or 4) 500 µg oral T4 followed by 100 µg PO daily	7 (2 in Group 1 and 5 in Group 2)	Laboratory values, clinical improvement	One patient died of myocardial infarction on Day 15 of treatment while receiving IV levothyroxine and cortisone therapy. One patient dies of septicemia on Day 9 of treatment while receiving oral levothyroxine.
Gavin, 1991 ^{xxxviii}	Myxedema coma	Review	Initial dose : T4 IV 500 µg IV Maintenance dose: T4 IV 50-100 µg daily	n/a	Laboratory values	Some systemic complications of myxedema coma may not respond rapidly to treatment. Cardio-respiratory dysfunction, hypothermia, and possible adrenal insufficiency should be monitored on an individual basis.
Smallridge, 1992 ^{xxxix}	Myxedema coma	Review	Initial dose: T4 IV 200-300 µg Maintenance dose: 50-100 IV µg/day	n/a	Laboratory values	Successful outcomes require careful monitoring in an intensive care unit.
Olsen, 1995 ^{xl}	Myxedema coma	Case series and review	T4 IV	1	Survival	A 90 year old woman was admitted with myxedema coma with metabolic derangements, possible heart failure, and a urinary

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Author	Indication studied	Literature category	Products used/recommended	No. of subjects	Primary endpoints	Safety/Tolerability Results
						tract infection. She was treated with no complications from IV therapy and was eventually discharged on oral levothyroxine.
Yamamoto, 1999 ^{xii}	Myxedema coma	Case series and meta-analysis	T4 IV at various doses, T3	8	Mortality	Mortality rate was highest after treatment with high dose LT3. Mortality rate was lowest with levothyroxine less than 500 µg daily.
Rodriguez, 2004 ^{xiii}	Myxedema coma	Review	High-dose: T4 500 µg IV Low-dose: no initial 500 µg IV bolus	High-dose: 6 Low-dose: 5	Mortality rate	Mortality rate was 36% (4 of 11 patients). There was much higher mortality among the group that did not receive an initial bolus (60% vs. 17%).

Key: IV=intravenous; µg=micrograms; TID=three times daily; IM=intramuscular; n/a=not applicable; ECG=electrocardiogram

Although for this Application, safety data were not gathered in a controlled trial setting and are derived from a variety of sources, the safety profile of IV levothyroxine can be delineated from the literature combined with the known profile of oral levothyroxine.

In general, the adverse event profile of levothyroxine emerges as it is excessively dosed. As such, the adverse event profile is consistent with hyperthyroidism: weight loss, increased appetite, palpitations, diarrhea, nervousness, sweating, abdominal cramps, tachycardia and elevated blood pressure, angina pectoris, tremors, insomnia, heat intolerance, fever, and menstrual irregularities.

Cardiac adverse events—myocardial ischemia and infarction, arrhythmias, congestive heart failure, and death—are more likely to occur with higher doses of the IV formulation and the submitted literature suggests this. There are several likely explanations for this. The intravenous doses used for the initial treatment of myxedema coma are larger than the average oral doses used in chronic levothyroxine therapy. Also, the typical patient diagnosed with myxedema coma is elderly with likely baseline cardiovascular disease. Finally, patients with myxedema coma appear to have numerous co-morbidities, increasing the likelihood of a fatal outcome even with levothyroxine treatment.

Beyond those already described, the adverse events reported within the literature consisted primarily of signs, symptoms, and laboratory abnormalities consistent with the underlying disease process. Patients with myxedema coma present with an underlying precipitating event, and therefore many of the terms noted include: hypothermia, cerebrovascular events, congestive heart failure, infections, sepsis, gastrointestinal bleeding, or generalized metabolic disturbances, as well as laboratory abnormalities of hypoglycemia, hyponatremia, acidosis, hypoxemia, and hypercarbia.

7.3.1 Deaths

The Sponsor provided a summary of deaths reported in the literature. Overall, myocardial infarction and sepsis were the common causes of death in this very sick patient population.

Table 4 Listing of Deaths in Reports Using IV Levothyroxine

Study/Lead Author	Dose of Levothyroxine and/or T3 Administered (µg)	Deaths Reported (% Mortality)
Bacci, 1981	800 µg IV levothyroxine	One death secondary to cardiac arrest 15 minutes after receiving an 800 µg IV bolus (100%)
Arlot, 1991	1000 µg IV levothyroxine	Two deaths: one due to a myocardial infarction on Day 15 after a large dose of IV levo and a second death due to sepsis on Day 9 of treatment (29%).
Yamamoto, 1999	50-1000 µg IV levothyroxine 5-200 µg T3	The highest mortality rate (60%) was seen in high dose T3 (>75 µg/day)

		cohorts. The lowest mortality rate (9%) was seen with lower doses of levothyroxine (<500 µg).
Rodriguez, 2004	100-500 µg IV levothyroxine	Four deaths were reported (36%). Mortality was in the group that received less than 500 µg compared with the group that received >500 µg.
Dutta, 2007	150-500 µg IV	Twelve patients died (12/21, 52%), with sepsis as the primary underlying factor.

Adapted from Sponsor's submission, Summary of Clinical Safety, Table 2.7.4-4

7.3.4 Significant Adverse Events

Cardiovascular related events from the literature were specifically examined by the Sponsor. Three studies specifically examined cardiac adverse events following IV levothyroxine to treat myxedema coma (Holvey, Arlot, Ridgeway). Two of the articles (Holvey, Ridgeway) did not observe any negative cardiac effects following treatment with doses of IV levothyroxine below 750 µg. The other (Arlot) observed negative cardiac effects following high doses of levothyroxine (1000 µg).

A case report from Bacci documented a cardiac arrest that occurred 15 minutes after the IV administration of a dose of 800 µg IV levothyroxine. Despite the patient's multiple comorbid conditions, at a minimum, the levothyroxine injection, one of the highest administered doses discussed in the literature, appeared to contribute to the cardiac arrest.

7.4 Supportive Safety Results

All available results from the submitted literature are reviewed above. This Section, therefore, will not include other specific findings, such as laboratory results and ECGs.

7.5.1 Dose Dependency for Adverse Events

The safety profile associated with the range of levothyroxine doses is discussed above. The literature suggests a worsening safety profile, particularly with regard to cardiovascular events and mortality, with initial IV doses exceeding 500 µg.

7.5.2 Time Dependency for Adverse Events

The time course of adverse events associated with hyperthyroidism depend on the dose and duration of drug administration. With regard to cardiovascular adverse events more closely linked to the IV levothyroxine formulation, because of the variability of presentations described, the literature is inadequate to characterize the time course of certain adverse events.

7.5.4 Drug-Disease Interactions

Thyroid hormone is essential for growth and development. As such, there are no diseases which contraindicate its use in the treatment of myxedema coma. However, because of potential cardiac toxicity, particularly with the IV formulation, treatment of both the elderly and patients with underlying cardiac disease who have myxedema coma should be initiated at the lower end of the recommended dose range.

7.5.5 Drug-Drug Interactions

For detailed comments regarding drug-drug interactions, see Clinical Pharmacology Review. A complete list interactions is discussed in Dr. Lau's label edits.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Levothyroxine, an endogenous hormone, does not have carcinogenic properties, even in excessive doses.

7.6.2 Human Reproduction and Pregnancy Data

There are no reported cases of IV levothyroxine used to treat myxedema coma in patients who were pregnant or lactating.

7.6.3 Pediatrics and Assessment of Effects on Growth

In the literature, there is only one report of a pediatric patient with myxedema coma.^{xliii} This occurred in the setting of cystinosis, a rare and life-threatening disease, in a 13 year old patient.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In the literature submitted by the Sponsor, there were no reported cases of overdose. However, intravenous doses above 500 µg are associated with cardiac complications, especially in those with underlying cardiac disease. Excessive doses of IV levothyroxine result in typical signs and symptoms of hyperthyroidism and thyrotoxicosis.

Levothyroxine is not associated with drug abuse, withdrawal, or rebound.

8 Postmarket Experience

The Sponsor accessed their postmarketing databases to compile a safety summary. Overall, the database contained only 2 events, both non-serious, reported to the company over a 7-year time period. The Sponsor also accessed the AERS database and found no safety reports associated with intravenous levothyroxine.

Finally, the Sponsor provided adverse event data for oral levothyroxine dosage forms. As that data is not pivotal to this application, it is not reviewed here.

9 Appendices

9.1 Literature Review/References

References are listed as endnotes.

9.2 Labeling Recommendations

At the time this Review was finalized, labeling recommendations with the Sponsor had not commenced. Below is a line-by-line review of the Sponsor's proposed label, which follows the comments.

Under HIGHLIGHTS, sections may need revision based on all recommendations for sections below.

Under HIGHLIGHTS, a boxed warning regarding its use for the treatment of obesity or weight loss should be included in all levothyroxine products should be added.

Under INDICATIONS AND USAGE, Sections should read:

- Section 2.1, Dosage
- Section 2.2, Dosing in the Elderly and in Patients with Cardiovascular Disease
- Section 2.3, Reconstitution Directions

All other Section headings under INDICATIONS AND USAGE should be deleted, as they are redundant, irrelevant, or discussed elsewhere in the label.

Under INDICATIONS AND USAGE "myxedema coma" (b) (4)

Under INDICATIONS AND USAGE, a "Limitations of Use" should be added to caution clinicians about switching from oral to IV levothyroxine. It should read as follows: "The relative bioavailability of this drug has not been established. Use caution when converting patients from oral to intravenous levothyroxine."

Under DOSAGE AND ADMINISTRATION, (b) (4)

(b) (4) Information in Section 2.4 regarding half-life and duration of treatment should be moved under 2.1.

Under DOSAGE AND ADMINISTRATION, the following statement should be added to provide limited bioavailability data for transitioning patients from IV to oral levothyroxine: “Relative bioavailability between Levothyroxine Sodium for Injection and oral L-thyroxine products has not been established. Based on published literature, absorption of the oral dose varies from 48-74% of the intravenous dose; since this is primarily due to differences in absorption characteristics of patients, appropriate thyroid function tests should be measured a few weeks after initiating oral L-thyroxine and dose adjusted accordingly.”

Under CONTRAINDICATIONS, should state “none” since there are no contraindications to treating a patient with myxedema coma.

Under WARNINGS AND PRECAUTIONS, Sections should read:

- Section 5.1, Use with Caution in Elderly and in Patients with Cardiovascular Disease
- Section 5.2, Use with Caution in Patients with Endocrine Disorders: this Section should include information regarding the use of replacement glucocorticoids when treating myxedema coma as well as the recommendation to monitor for undiagnosed diabetes insipidus.
- Section 5.3, Observation of Patient Following Administration
- Section 5.4, Not Indicated for Treatment of Obesity: this should reiterate information from the Black Box Warning.

Under ADVERSE REACTIONS, remove the statements

(b) (4)



Under USE IN SPECIFIC POPULATIONS, Section 8.5 should be re-titled “Geriatric Use and Patients with Underlying Cardiovascular Disease”. This Section should specifically mention “atrial fibrillation” as a risk in the elderly.

Under OVERDOSAGE

(b) (4)

Under OVERDOSAGE, Treatment of Overdosage,

(b) (4)

Reference should be made to the Poison Control Center.

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NAOMI N LOWY
05/12/2011

DRAGOS G ROMAN
05/12/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	See comment under #14.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		At pre-NDA meeting, Sponsor mentioned that they intend to apply for a waiver. DMEP told them that PeRC would need to be consulted.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? yes

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Internal Comments and Conclusions: This 505(b)(2) application relies completely on literature to support the safety and efficacy of levothyroxine injection, which is currently an unapproved, marketed drug. The Sponsor, APP Pharmaceuticals, is currently the sole source of levothyroxine injection and therefore is supplying all demand of this medically necessary drug. Given this, it appears that from a filing perspective, the Sponsor has submitted sufficient literature to conduct a review of appropriate dosing, including information on bioavailability compared to an oral levothyroxine formulation. Comments to the Sponsor that are not filing issues are listed below.

Clinical Comments to be Conveyed to Sponsor:

Labeling

1. We acknowledge your proposed indications of “myxedema coma, (b)(4)
[Redacted]
2. Dosage and Administration instructions include the recommendation to use 0.9% Sodium Chloride Injection, USP (b)(4)
[Redacted]

Naomi Lowy, M.D. October 18, 2010

Reviewing Medical Officer Date

Dragos Roman, M.D. October 18, 2010

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NAOMI N LOWY
10/19/2010

DRAGOS G ROMAN
10/19/2010