

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202231Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	June 2, 2011
From	Dragos Roman MD
Subject	Cross-Discipline Team Leader Review for an intravenous levothyroxine product
NDA/BLA #	202-231
Supplement#	0
Applicant	APP Pharmaceuticals, LLC
Date of Submission	August 30, 2010
PDUFA Goal Date	June 30, 2010
Proprietary Name / Established (USAN) names	Levothyroxine Sodium for Injection/ Levothyroxine Sodium for Injection
Dosage forms / Strength	Three presentations containing the following strengths of levothyroxine sodium: 100 mcg/6.5 mL vial, 200 mcg/10 mL vial, 500 mcg/10 mL vial
Proposed Indication(s)	Treatment of myxedema coma
Recommended:	Approval

1. Introduction

Levothyroxine Sodium for Injection is a marketed unapproved drug used for the treatment of myxedema coma and other forms of hypothyroidism in which oral levothyroxine administration is not feasible. On December 18, 2006, APP Pharmaceuticals, the manufacturer of Levothyroxine Sodium for Injection (and sole manufacturer of an intravenous levothyroxine product at this time), was notified via a Warning Letter issued by the FDA Chicago District that, in order to lawfully market this product, it will need to submit a New Drug Application. A pre-IND meeting was held with the Agency on March 18, 2008, at which time APP Pharmaceuticals received advice from multiple review disciplines. Specifically, FDA requested that, given the diversity of information available in the medical literature, the company provide a clear justification for the proposed dosing regimen to be labeled for the treatment of myxedema; in addition, the Agency requested relative bioavailability data between oral and intravenous (IV) levothyroxine to guide dose conversion between these two regimens.

APP Pharmaceuticals submitted the current NDA (202-231) on August 30, 2010 under Section 505(b)(2) of the Food, Drug, and Cosmetics Act. The preclinical, clinical pharmacology, and clinical sections of the NDA contain exclusively data derived from published literature. From an approvability standpoint two issues are central to this submission: 1) the demonstration that the drug substance specifications (including identity, purity, excipient characterization) meet Agency standards, and 2) whether the literature published with intravenous levothyroxine in

myxedema coma is sufficient to identify a safe and effective treatment regimen, and if such information can be organized in a cohesive and informative label.

2. Background

Levothyroxine has a very long history of use in humans. Following the discovery of thyroxine in 1914, the elucidation of its chemical structure in 1926 and its subsequent synthesis, it has been used as replacement therapy for more than half a century. Intravenous formulations of levothyroxine have been introduced in the treatment of myxedema coma in the early 1960's.

The basic physiology of levothyroxine has been largely elucidated and is relatively well understood. This knowledge has its origins in an extensive body of medical literature spanning multiple decades of investigations and its therapeutic use is summarized in standard textbooks and professional society guidelines (e.g. Endocrine Society, American Thyroid Association). Although there are obvious differences between oral and IV levothyroxine products, mostly related to the route of administration, rate of absorption, and specific dosing, the clinical effect can be largely extrapolated from oral to intravenous products. No less importantly, the toxicity profile of levothyroxine in humans is well characterized on the basis of medical conditions of thyroid hormone excess or inappropriate use.

Myxedema coma is the most severe form of hypothyroidism. It is an exceedingly rare medical condition - an incidence rate of 0.22 per 1,000,000 per year has been reported - with an associated mortality as high as 80% if left untreated. There are only approximately 300 cases of myxedema coma reported to date in the medical literature.

At the time of NDA submission the applicant proposed the following indication:

L-Thyroxine for Injection is indicated for treatment of myxedema coma, (b) (4)

The Division took the position that (b) (4)
The applicant agreed and, in an amendment dated May 13, 2001, stated that "that the only indication to be listed on the drug product labeling is myxedema coma".

3. CMC/Device

The drug substance for Levothyroxine Sodium for Injection is levothyroxine, identical in structure with the eponymous hormone. The drug product is a lyophilized powder containing levothyroxine sodium along with the following excipients: dibasic sodium phosphate heptahydrate, mannitol, and sodium hydroxide. It is packaged in amber glass vials (the drug product is photolabile) at three dosage strengths: 100 mcg/vial, 200 mcg/vial and 500 mcg/vial, and is stored at room temperature. These three dosage forms were selected with the goal of supporting a range of loading doses of 300-500 mcg and maintenance doses of 50 mcg and 100 mcg. Once reconstituted in 0.9% sodium chloride for injection, the product is to be used immediately (it is, in fact, stable for up to 4 hours at room temperature).

The drug substance specifications were found to be acceptable by the CMC reviewer and they met all the requirements of the current USP monograph, as did all the excipients. In addition, all impurities met compendial requirements as well. A shelf-life of (b) (4) was granted for storage at room temperature (b) (4) because of insufficient real-time stability data.

There are no CMC issues to prevent approvability. Both the primary CMC review (Dr. Leginus; DARRTS 4/29/2011) and secondary review (Dr. Al Hakim; DARRTS 4/29/2011) recommend approval of the application, and there are no requests or recommendations for postmarketing studies. The microbiology review also recommends approval, indicating that no deficiencies were identified regarding the sterility of the drug product. Finally, the CMC review also indicates that “acceptable cGMP recommendations have been received from the Office of Compliance for all manufacturing and testing facilities.”

4. Nonclinical Pharmacology/Toxicology

The applicant did not conduct any pharmacology, pharmacokinetics, or toxicology animal studies with Levothyroxine Sodium for Injection. Instead, the nonclinical data presented in this application summarizes information from published literature, most of which was obtained with levothyroxine administered via routes other than IV. The reviewer comments that in the absence of toxicokinetic information it is difficult to predict human exposure and toxicity. On the other hand, the absence of a clear relationship between toxic animal doses and proposed human doses is counterbalanced by information provided by clinical experience in humans (which is quite extensive), by the fact that IV levothyroxine is administered to patients in a controlled hospital setting for a condition characterized by low or absent endogenous levothyroxine and, very importantly, by the mode of administration which involves titration to a desired pharmacodynamic and clinical response.

It is anticipated that the toxicity profile of intravenous levothyroxine in humans will be dictated by the exaggerated pharmacological effect of levothyroxine (i.e. symptoms of hyperthyroidism) and/or the impurity profile. While with respect to the former, appropriate

human dose selection and careful clinical monitoring should prevent such toxicity. Regarding the latter, the impurities identified in the drug product were all found to be within acceptable limits, and no animal studies were felt to be needed in order to further characterize them. In final analysis, the pharmacology/toxicology reviewer recommends approval of Levothyroxine Sodium for Injection for the treatment of myxedema coma.

In addition, one needs to acknowledge that the role of a preclinical toxicology program for a product whose active moiety is a small molecule identical structurally to an endogenous hormone, as is the case with levothyroxine (or other hormones for that matter), is different when compared to a chemical compound for which there is no human counterpart. Such difference exists not only because we understand better the physiological and pharmacological effects of a native product but, even more so, because of the availability of human “toxicology” data provided by pathological conditions of hormone excess, such as hyperthyroidism. In such cases the CMC confirmation of identity and purity is a considerable step in providing reassurance on the safety of the product.

5. Clinical Pharmacology/Biopharmaceutics

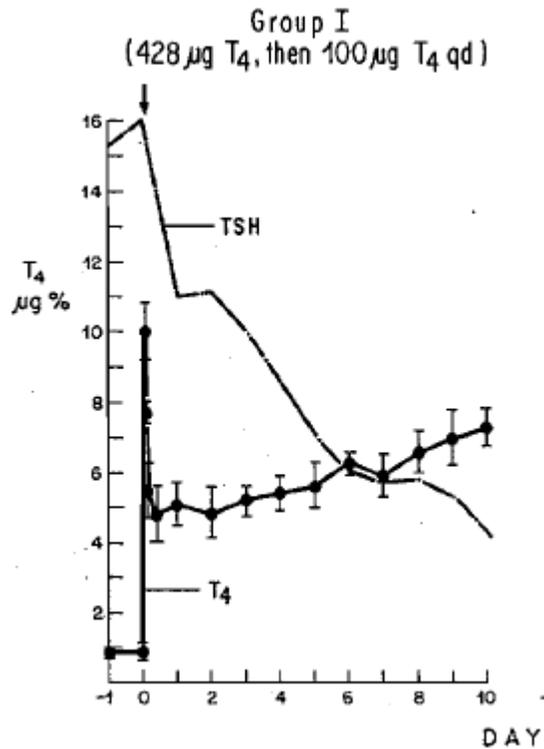
The clinical pharmacology review recommends approval of the application. As was the case with the preclinical pharmacology/toxicology section of the submission, the applicant did not conduct any clinical pharmacology studies, relying instead exclusively on published literature.

Analysis of the published information indicates that, once injected, levothyroxine distributes rapidly to target tissues and is indistinguishable from endogenous levothyroxine. It has a relatively long half-life (6 – 8 days for euthyroid patients and 9 – 10 days for myxedema patients) primarily due to the fact that > 99% of plasma levothyroxine is protein bound, which protects it from rapid degradation and excretion. Only unbound hormone is metabolically active. The major metabolic pathway of degradation is sequential deiodination that occurs in the thyroid, liver, kidneys, placenta and fibroblasts. Another route of degradation is hepatic glucuronidation and sulfation, followed by excretion into the bile and intestine from which it can be recirculated enterohepatically. The major route of excretion is renal, and only 20% is eliminated in the stool.

The pharmacodynamic response in myxedema coma is illustrated in Figure 4 of the clinical pharmacology review¹, which depicts the time course of TSH reduction following the administration of a levothyroxine dose (428 mcg) at the upper end of the proposed levothyroxine starting dose (300-500 mcg). A 32% reduction in TSH of is observed within 24 hours of IV levothyroxine administration; the TSH reduction continued during maintenance

¹ Reproduced from Ridgeway EC, McCammon JA, Benotti J, et al. Acute metabolic responses in myxedema to large doses of intravenous L-thyroxine. *Ann Intern Med* 1972;77:549-555.

treatment with subsequent daily intravenous doses of 100 mcg of levothyroxine (the proposed regimen is 50-100 mcg).



The clinical pharmacology review addresses at length the issue of relative bioavailability (BA) of oral levothyroxine and IV levothyroxine and whether a BA study with an approved oral levothyroxine product is necessary for approval. The review points out that under CFR 320.21 there is a regulatory requirement for providing bioavailability information. The review also emphasizes the importance of having accurate information for converting the intravenous levothyroxine dose to an oral levothyroxine dose.

In the end, the clinical pharmacology reviewer recommends waiving the requirement for a BA study “for good cause” (CFR 320.22(e)). I agree with this recommendation which is made with the explicit goal of ensuring an uninterrupted supply of IV levothyroxine to physicians who treat patients with myxedema coma, a true endocrine emergency with mortality as high as 80% if left untreated. On the other hand, my *stricto sensu* reading of the regulations is that under 320.21 in vivo bioavailability can be waived for products for which bioavailability is self-evident, as is the case of “a parenteral solution intended solely for administration by injection” (which appears to be the specific case for Levothyroxine Sodium for Injection).

With respect to the issue of conversion of the intravenous dose to an oral dose, I agree with the point made that a bioavailability study with a currently marketed oral formulation is desirable, but it needs to be acknowledged that in the clinical setting conversion of IV levothyroxine to oral levothyroxine is not an issue since the clinical norm is to use a conversion ratio of 1:2.

This 50% conversion rule is a rather conservative approach, some references² indicating a 66% to 72% relative bioavailability with older oral levothyroxine products. Equally important, this dose conversion is not expected to provide an “ultimate” oral dose but rather a transition regimen that is further adjusted, optimized and individualized by titration to biochemical and clinical response, depending on the underlying etiology of hypothyroidism.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The evidence of efficacy is provided exclusively from published literature and consists mostly in case reports, case series, meta-analyses, and reviews, and only occasionally prospective data; as such, there is no statistical review for this application. Dr. Lowys’s clinical review refers to 45 literature articles that the applicant submitted to support a determination of efficacy for Levothyroxine Sodium for Injection in myxedema coma (12 of them refer primarily to either oral levothyroxine or to triiodothyronine). Given that in myxedema coma levothyroxine is used to replace a missing or insufficient endogenous hormone, the central issue from a clinical standpoint is that of identifying a dose regimen that reverses the state of deficiency, while delivering a dose free of the known toxicities associated with levothyroxine excess. Therefore, this section of the memorandum will touch on both efficacy and safety issues. This memorandum will not reiterate the arguments that support the superiority of intravenous levothyroxine regimens over intravenous triiodothyronine regimens; this issue is not directly related to the proposed labeling claims of this particular application; it is, however, of general interest and is discussed by Dr. Lowy in the clinical review.

The published literature provides ample and convincing evidence that intravenous levothyroxine is an effective treatment for myxedema coma. Intravenous levothyroxine has changed the outcome for myxedema coma from a mortality rate up to 80% to approximately 80% survival (data vary between different reports depending of the severity of myxedema at the time of intervention, the presence and the severity of comorbidities, and the specific dosing regimen selected). Several dosing regimens have been investigated since the early 1960s when the efficacy of intravenously administered levothyroxine was demonstrated in a study in which all seven patients with myxedema coma survived after receiving 120-500 mcg (average dose 411 mcg) of levothyroxine³. Historically, the initial dose regimens have been selected on the basis of information accumulated from basic physiology studies which allowed an estimation of a total body pool of levothyroxine of 360 mcg and a daily turnover of 50-80 mcg in

² Maxon et al. (*Int J Clin Pharmacol Ther Toxicol* 1983;21:379-82)

³ Holvey DN, Goodner CJ, Nicoloff JT, et al. Treatment of myxedema coma with intravenous thyroxine. *Arch Intern Med* 1964;113:89-96.

euthyroid patients. Based on such information, patients received levothyroxine doses that attempted to meet physiological needs or replace deficits. For instance, a 500 mcg loading dose was estimated to restore levothyroxine levels to about half of the euthyroid value and such a dose and higher doses (e.g. 750 - 1000 mcg) were investigated⁴. Following administration of an intravenous loading dose of levothyroxine, clinical changes in vital signs are noticed after 6-12 hours; due to the long half-life of the hormone, peak metabolic effect occurs after 10-12 days.

Once clinical experience has accumulated, it became evident that loading doses > 500 mcg were in fact excessive, did not provide additional efficacy benefits, and were associated with undesired adverse events, particularly coronary ischemia, myocardial infarction, and arrhythmias. Additional data indicated that some subgroups of patients, such as the elderly and patients with underlying cardiac disease, while not having different efficacy requirements, were at higher risk for severe outcomes, and conventional wisdom dictated that in such patients treatment should be initiated at the lower end of the effective doses. The consensus that is emerging among authors is that doses > 500 mcg daily are unsafe and that lower dose regimens (300-500 mcg or even lower) are desirable. It is in fact a loading dose of 300-500 mcg that the applicant proposes for the Levothyroxine Sodium for Injection label, and in her review Dr. Lowy concurs.

Following the selection and administration of a loading dose, levothyroxine treatment continues with a daily “maintenance” intravenous dose for a variable period of time until patients recover enough to be considered for oral levothyroxine replacement; at that time the IV dose is converted to an equivalent oral dose. Although the issue of selecting maintenance doses is discussed less frequently in the published literature (conceivably because a narrower range of doses and less controversial dosage regimens have been explored), there appears to be general agreement that daily maintenance doses of 50-100 mcg are effective and reasonably safe. The conversion of the IV levothyroxine dose to an oral dose has been already discussed in Section 5 of this memorandum.

It should be also recognized that transition from IV levothyroxine to oral administration during the treatment of myxedema coma is different from converting an oral levothyroxine product to IV levothyroxine in a patient who is currently euthyroid but cannot receive oral thyroxine because of an intervening condition that precludes oral drug administration (e.g. severe or persistent gastrointestinal illness, surgery, critical illnesses, etc). In such situations a more precise knowledge of levothyroxine’s bioavailability will be necessary to prevent under- or over-estimating the IV dose, which in either scenario may have serious clinical consequences to the patient. This is a situation that may be encountered in clinical practice and, until the applicant conducts a bioavailability study to address this issue, a limitation of use should be included in the drug label to make prescribers aware of this existing dosing limitation. Should the sponsor conduct a relative bioavailability study in euthyroid patients, and should such a study be approved, the limitation of use will no longer be necessary and should be removed from the label. (b) (4)

⁴ Ridgeway EC, McCammon JA, Benotti J, et al. Acute metabolic responses in myxedema to large doses of intravenous L-thyroxine. *Ann Intern Med* 1972;77:549-555.

8. Safety

Generally speaking, the human toxicity profile of Levothyroxine Sodium for Injection is expected to be that of hyperthyroidism⁵ if the product is administered at excessive doses. In this context, the known effect of levothyroxine on cardiovascular function, which may result in tachycardia, arrhythmias, myocardial ischemia and infarction, or worsening of congestive heart failure, is of particular importance. These complications are expected to be an issue particularly in patients with underlying cardiac disease and in the elderly, who have a limited cardiac reserve.

The safety information submitted in this NDA confirms the above expectations. The NDA summarizes safety data from 40 clinical studies, although not all of them were specific to the IV delivery route. It is noteworthy that loading doses as high as 1000 mcg had been used before the safety profile of IV levothyroxine was established. An increased risk of cardiovascular adverse events with doses greater than 500 mcg is amply documented and therefore such excessive doses should not be approved (see also Dr. Lowy's analysis of the published safety information in Table 3 titled "Clinical Safety Studies Reported in the Literature" and Table 4, "Listing of Deaths in Reports Using IV Levothyroxine"). The dosing regimen already discussed in Section 7 of this memorandum already reflects these safety concerns, including those specific to the elderly and to patients with coexisting cardiac disease.

In recognition of the fact that the dose regimen needs to be individualized, the "Dosage and Administration" Section of the label has language indicating that age, general physical condition, cardiac risk factors, and clinical severity of myxedema and duration of myxedema symptoms need to be considered when determining the starting and maintenance dosages of Levothyroxine Sodium for Injection. In addition, reflecting the safety observations made in different patient populations, the Warning and Precautions Section of the label indicate that in patients at risk (elderly and those with existing cardiac disease) dosing has to be started cautiously. I do not believe that these warnings should be carried further into a Boxed Warning because patients with myxedema coma are cared in specialized settings with good monitoring (ICUs) by highly qualified and knowledgeable practitioners.

Finally, I am in agreement with Dr. Lowy that the dose regimen proposed reaches a reasonable balance between safety and efficacy.

⁵ Palpitations, tachycardia, nervousness, tremors, insomnia, heat intolerance, sweating, abdominal cramps, diarrhea, increased appetite, elevated blood pressure, angina pectoris, fever, menstrual irregularities, weight loss, etc.

9. Advisory Committee Meeting

There were no Advisory Committee meetings

10. Pediatrics

The application received a waiver for pediatric studies under PREA because myxedema is exclusively an adult disease without a pediatric counterpart.

11. Other Relevant Regulatory Issues

None.

12. Labeling

A final labeling has been negotiated with the applicant and will not be reproduced in this memorandum. The relevant efficacy, safety and dose-selection comments made in this memorandum have been addressed in the label.

13. Recommendations/Risk Benefit Assessment

Levothyroxine Sodium for Injection should be approved for the indication of treatment of myxedema.

- Risk Benefit Assessment

The risk benefit ratio is favorable for the proposed dosing regimen (300-500 mcg initial loading dose followed by 50-100 daily mcg administrations until patients have recovered and are expected to tolerate oral levothyroxine). As indicated in the body of this memorandum (and reflected in the finalized drug label) it is recommended that this dosing regimen be individualized, particularly in patients with risk factors such as advanced age and existing cardiovascular disease.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

None.

- Recommended Comments to Applicant

Because your application did not provide enough information to guide conversion from an oral to an intravenous (IV) levothyroxine regimen for hypothyroid patients who are controlled on oral levothyroxine products but require temporarily IV replacement, as discussed in the May 11, 2011 teleconference, we encourage you to conduct a bioavailability study addressing the issue of oral to IV dose conversion. The results of such a study may be submitted as an efficacy supplement (b) (4)

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/s/

DRAGOS G ROMAN
06/02/2011

MARY H PARKS
06/02/2011
Concur with Dr. Roman's recommendations