MEMORANDUM

DATE: 8/17/00

TO: NDA 21-210, Levothyroxine Sodium Tablets, USP, Jerome Stevens Pharmaceuticals, Inc.

FROM: Elsbeth G. Chikhale, PhD, chemist reviewer, HFD-820

SUBJECT: Immediate container and carton label

The revised proposed immediate container and carton labels, faxed to the Agency on 8/17/00, have been reviewed and found acceptable. There are no remaining chemistry issues.

Memorandum to File

To: NDA 21-210 file
From: S. Markofsky (Acting Team Leader)
Subject: Storage Statement for Jerome Sevens Pharmaceutical's Levothyroxine Sodium (Tablets)
Date: 8-4-00

In the labeling provided in NDA 21-210 for their Levothyroxine Sodium (Tablets), Jerome Sevens Pharmaceutical's proposed the following storage statement:

"Store at controlled room temperature 150-300C (59-860F)"

The Chemistry Reviewer for this NDA (Elsbeth Chikhale), with the concurrence of the Chemistry Team Leader (Duu-Gong Wu) has suggested that the storage temperature should be changed to:

"20°-25°C (68°-77°F) with excursions between 15° and 30°C (59°-86°F)"

At a meeting on the status of this NDA (8-1-00), a question was raised about the appropriateness of the storage statement that was suggested by the Chemistry Reviewer, in view of possible conflicts with the Agency's Stability Guidance and ICH proposals. I believe our suggested statement is appropriate for the following reasons:

1) Stability studies were conducted at 25°C/60%RH. No data was provided from samples of the drug products stored at 30°C.

2) The CDER Chemistry, Manufacturing and Controls Coordinating Committee (CMC CC) has taken issue with the ICH proposal. The CMC CC,s opinion was described in a "Preliminary Position Paper" on the subject, dated 9-13-96. The CMC CC position can be illustrated by the following statement, taken from the "Position Paper":

Stability studies done under the ICH conditions of 25°C/60% RH can not support continuous, long-term storage of a product at 30°C. Thus, statements like "store below 30°C", "store up to 30°C," or "store between 15 and 30°C", are no longer appropriate by themselves.

There is no new official Agency position on this subject. (The Stability Guidance is out for comment and has not yet been approved.)

3) Temperature related stability problems are well known for Levothyroxine Sodium ; therefore, storage at 30°C should be discouraged.

4) Our suggested storage statement has been discussed with Robert Seevers (Chairman of the Stability Committee), John Gibbs (Div. Dir. for DNDC II), and Yuan-Yuan Chiu (Office Dir. of ONDC); and they all agree that our suggested storage statement is appropriate.

Sheldon Markofsky
(Acting team Leader for Duu-Gong Wu)

MEMORANDUM

DATE: August 20, 2000

FROM: John K. Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Director
Office of Drug Evaluation II, HFD-102

TO: NDA 21-210

SUBJECT: Overview of review issues

Administrative

NDA 21-210 for UNITHROID (levothyroxine sodium tablets) was submitted by Jerome Stevens Pharmaceuticals on October 19, 1999. This application was submitted in response to the August 14, 1997, Federal Register Notice announcing that orally administered drug products containing levothyroxine sodium are new drugs. The FR notice required that sponsors who wished to continue to market orally administered drug products containing levothyroxine sodium have an approved NDA by August 14, 2000 (this date was recently extended to August 14, 2001). This NDA was assigned for a standard review. The 10-month user fee due date for this application is August 21, 2000.

Clinical/Statistical

The 1997 FR notice stated that the active ingredient, levothyroxine sodium, is effective in treating hypothyroidism and is safe when carefully and consistently manufactured and stored, and prescribed in the correct amount to replace the deficiency of thyroid hormone in a particular patient. Therefore, no clinical safety and effectiveness studies were required to support approval of these formulations, only a submission of literature references to support the safety and effectiveness of levothyroxine sodium. The sponsor submitted a review of the available literature for this purpose. Please refer to the review prepared by Dr. Temeck for a detailed review of the available literature on the safety and effectiveness of levothyroxine sodium (including Dr. Temeck's own extensive and comprehensive review of the published literature on this topic).

This application is approvable from a clinical/statistical perspective with labeling as developed for this individual product based on the standardized labeling for levothyroxine drug products developed by the Division.

Pharmacology/Toxicology

No preclinical studies were included in the NDA and none were required given the long marketing history of levothyroxine containing products and the determination as stated in the 1997 FR notice that the active ingredient, levothyroxine sodium is safe and effective when manufactured, stored, and prescribed correctly. The inactive ingredients in the UNITHROID tablets do not raise any new safety issues. The sponsor submitted literature references to address preclinical sections of labeling.

This application is approvable from a pharmacology/toxicology perspective with labeling incorporating the preclinical sections of the levothyroxine standardized labeling developed by the Division.

Chemistry, Manufacturing, and Controls

The sponsor proposes to market tablets containing 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg. Please see the review prepared by Dr. Chikhale for a detailed review of the CMC information provided by the sponsor. The information provided by the sponsor has been found acceptable for the drug substance, the drug product, and packaging materials. The stability data were generated under ICH storage conditions and support an initial 18-month expiration dating for all tablet strengths. The sponsor will submit additional data, as they become available, to further extend the expiration date. The sponsor has also made a phase 4 commitment to explore the development of an improved test(s) to monitor degradation products and to include the test and specification in the stability protocol within a year after NDA approval. This is acceptable as a phase 4 commitment since the sponsor is already monitoring degradation products in compliance with the current USP monograph.

This application is approvable from a CMC perspective with labeling as agreed based on the modified levothyroxine standardized labeling and with the above mentioned phase 4 commitment.

Clinical Pharmacology and Biopharmaceutics

The Agency's guidance for submission of an NDA for orally administered levothyroxine drug products recommended two in vivo BA/BE studies (a comparison of the tablet formulation to an oral solution and a comparison of low, medium, and high strength tablets) and in vitro dissolution studies. These studies were submitted by the sponsor. Please refer to the review prepared by Dr. Johnson for a detailed review of these studies. In summary, the tablet formulation was demonstrated to be equivalent to an oral solution of levothyroxine sodium and the 50 mcg, 100 mcg, and 300 mcg tablets were demonstrated to be equivalent to each other. The sponsor also submitted dissolution data using USP 23 for three lots of each tablet strength. These data were found acceptable and a specification of 55% (Q) in 80 minutes has been established.

The sponsor has agreed to a phase 4 commitment to develop dissolution data using the new USP 24 methodology, which went into effect as of January 2000. After an internal discussion including representatives from OCPB and ONDC, it was agreed that the

sponsor could maintain the "USP" designation on the product labeling despite not having used USP method 24 to conduct their dissolution testing. This decision was based on the fact that once a new USP method is introduced, there is usually a "grace" period for sponsors to meet the new testing standard. For further assurance, the sponsor was asked to submit data on lots of finished drug product that had been tested using USP 24 methods. The sponsor submitted data for 5 finished lots and all lots passed the USP 24 specifications (see Dr. Chikhale's memo dated August 18, 2000).

This application is approvable from a biopharmaceutics and clinical pharmacology perspective with labeling as modified for this specific product based on the levothyroxine standardized labeling developed by the Division and with the phase 4 commitment related to USP 24 dissolution data as noted above.

Data Integrity

The Division of Scientific Investigations audited the analytical portions of the two pivotal BA/BE studies. Minor deficiencies were noted in the conduct of both studies and a VAI rating was assigned. These deficiencies are not felt to adversely affect the interpretation of the data derived from these studies.

Labeling and Nomenclature

The sponsor has proposed the tradename UNITHROID for this product. This name is acceptable to the Division and to OPDRA. Since there are expected to be numerous applications for orally administered levothyroxine drug products in response to the 1997 FR Notice and since most of the information that will be included in labeling will be based on literature references, the Division has developed standardized labeling for these products that will be individualized as appropriate for each sponsor (e.g., Description, How Supplied, PK sections). The draft labeling as submitted by the sponsor is acceptable and accurately reflects the data submitted in the NDA and the available data from the literature regarding the safe and effective use of levothyroxine sodium.

Conclusions

This NDA should be APPROVED with draft labeling as submitted by the sponsor and agreed to by the Division. The sponsor will be reminded of their two phase 4 commitments as noted above in the action letter.