2632 5 JUL 22 A9:54

MYLAN LABORATORIES INC.
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, WV 26504-4310 U.S.A. • (304) 599-2595

July 21, 2005

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

RE: Comments Pertaining to the Joint Public Meeting on Equivalence of Levothyroxine Sodium Products, Held on May 23, 2005, Docket No. 2005N-0137

Representatives from Mylan Laboratories both attended and participated in the May 23, 2005, Joint Public Meeting regarding the equivalence of levothyroxine sodium products, co-sponsored by the FDA, the American Thyroid Association, the Endocrine Society and The American Association of Clinical Endocrinologists. Mylan has a vested interest in the topics discussed at this meeting as our company currently has approval for and markets a generic levothyroxine sodium product, which has been shown to be bioequivalent to Unithroid®[1], Synthroid®[2], and Levoxyl®[3].

Pharmacokinetic Considerations

Mylan Laboratories, through its wholly owned subsidiary Mylan Pharmaceuticals, has been developing, manufacturing, and marketing generic drug products for many years and Mylan has a long history in working with the FDA's bioequivalence requirements. Mylan supports and agrees with FDA's bioequivalence guidelines for determining the therapeutic equivalence of orally administered drug products, including levothyroxine sodium products. The endocrine societies, on the other hand, appear to have concerns about accepting these well-accepted FDA standards. At the May 23, 2005 meeting, these societies expressed that they wanted more stringent bioequivalence (BE) requirements, the utilization of thyroid stimulating hormone (TSH) as a marker for BE determination, stricter labeling warnings regarding switching between brands of levothyroxine sodium products along with wording around monitoring of TSH levels following a switch, and the use of controlled crossover clinical trials in athyrotic patients to prove BE between products. Mylan Laboratories disagrees with the suggestions put forth by the societies.

[1] Unithroid® is a registered trademark of Jerome Stevens Pharmaceuticals Inc.
[2] Synthroid® is a registered trademark of Knoll Pharmaceutical Company.
[3] Levoxyl® is a registered trademark of Jones Pharma Incorporated.

2005N-0137 C5

First, Mylan would like to dispel the preconceived notion the endocrine societies seem to have regarding the results of a BE study. The FDA states that for the natural log transformed parameters associated with the rate and extent of absorption (area under the curve from zero to the last detectable concentration, AUCL; area under the curve from zero to infinity, AUCI; and the maximum plasma concentration, Cmax), the 90% confidence intervals must fall between 80 and 125% for therapeutic equivalence. This does not infer that the amount of levothyroxine sodium contained within the tablet can vary by 20%. It should be noted that manufacturing limits for assay are rigidly set to +/- 10% of label claim. And in fact, the FDA bioavailability and bioequivalence guidance states that the test and reference products being investigated in a BE study can not vary in active ingredient composition by more than 5%.[4] The 90% confidence interval reflects a statistical probability that ninety percent of the time the investigated population mean test to reference ratio for that pharmacokinetic parameter will fall within that observed confidence range. Furthermore, FDA has refined its BE guidance specific to levothyroxine sodium tablets in that plasma levothyroxine (T4) concentrations are corrected for average pre-dose baseline concentrations prior to pharmacokinetic parameter determinations.

Mylan has conducted three single-dose randomized cross-over BE studies assessing the therapeutic equivalence of our 300 μg tablets to three different new drug application (NDA) sponsored products (refer to Attachment A for data summary). These results help to illustrate the high degree of equivalency by which the Mylan product matches the various NDA sponsored products. Mylan believes that with the inherent variability that exists between lots of an NDA sponsored levothyroxine product, that the variability observed for these studies and allowed by the FDA in their current BE guidelines is appropriate and should not be altered.

The suggestion of utilizing TSH to determine BE between two levothyroxine sodium products is erroneous. Granted, it may be the most utilized parameter to assess the status of a patient's thyroid function/disease state by a physician. However, utilizing this biomarker as a factor in assessing the rate and extent of absorption of two different formulations of levothyroxine sodium in a quantitative and scientific manner is flawed. TSH has a diurnal rhythm with low levels typically during the day and high levels at night with a subsequent pulsatile release pattern.[5] TSH has more variability than T4, which is what the FDA utilizes to prove therapeutic bioequivalence. For example, in the Vaisman et al. study, T4 area under the curve from zero to 24-hours after dosing had a percent coefficient of variation (CV%) of about 14%, while TSH had a CV% of approximately 100%.[6] Similar results were obtained in the Dong et al. study.[7] Obviously

---

[4] FDA "Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations". March 2003.

[5] Weeke J and HJG Gundersen. "Circadian and 30 minute variations in serum TSH and thyroid hormones in normal subjects". *Acta Endocrinologica.* 89: (1978), 659-672.

[6] Vaisman M, Spina LDC, Eksterman LF, dos Santos MJCF et al., "Comparative Bioavailability of Two Oral L-Thyroxine Formulations after Multiple Dose Administration in Patients with Hypothyrodism and its

if we use a highly variable measurement like TSH the confidence limits will need to be widened or, as Dr. Lesko commented, "Nothing will pass 80-125%".[8] Assessment of baseline-corrected T4 provides a direct measure of product performance, which is directly linked to the active product.

In addition, TSH levels can vary depending upon the season of the year the study was conducted.[9] With T4 having an elimination half-life of around 6 to 7 days[10], it will require a washout period of at least five weeks in between dosing periods of a bioequivalence study. With such a long washout period, temperature fluctuations could become an uncontrollable factor influencing the results of a bioequivalence study if TSH was the parameter being utilized to prove therapeutic equivalence. The emotional state of the subject can also influence TSH levels.[9] With such uncontrollable influences as climate temperature and emotional status of the subject, the use of TSH for the determination of therapeutic equivalence between two levothyroxine sodium products is not of sound scientific merit. The determination of therapeutic equivalence should be based upon a parameter that is not only quantitative, but is reproducible regardless of environmental and emotional conditions. The FDA met these criteria when it proposed the utilization of a 600 µg dosage administration of levothyroxine sodium tablets and testing for the rate and extent of absorption of T4.

Based upon the summary basis of approval (SBOA) for the NDA sponsored levothyroxine sodium products, the FDA granted approval based upon non-baseline corrected T4 rate and extent of absorption measurements.[11] TSH was not utilized, according to the SBOA, nor was it even assessed by the NDA sponsor during their studies.[11] Due to the lack of any definitive evidence by the endocrine societies, showing safety issues with the approved products, it is preposterous to require assessment of therapeutic equivalence based on the highly variable TSH measurement.

The choice of utilizing athyrotic subjects for conducting a BE study is also not a reasonable proposal, as it poses some ethical dilemmas. These individuals rely solely upon exogenous sources of thyroxine to maintain a euthyroid state, thus differences in the rate and extent of absorption between two formulations of levothyroxine sodium could be

---

Relation with Therapeutic Endpoints and Dissolution Profiles," Arzneim.-Forsch./Drug Res. 2001, 51:246-252.

[7] Dong BJ, Hauck, WW, Gambertloglio JG, Gee L, White JR, Bubp JL and Greenspan FS, "Bioequivalence of Generic and Brand-name Levothyroxine Products in the Treatment of Hypothyroidism," JAMA 1997, 277:1205-1213.

[8] Dr. Lesko comments from the Advisory Committee for Pharmaceutical Science Minutes, March 2003, p. 204.

[9] Guyton AC. Human Physiology and Mechanism of Disease, 5th Ed. Philadelphia: WB Saunders Co., 1992.

[10] Synthroid® Package Insert, Abbot Laboratories Inc., July 2002.

[11] http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm for Synthroid®, Unithroid®, Levoxyl®, Levo-T®, Levolet®, Thyro-Tabs®, and Novothyrox®.

discerned in this population. However, during the investigative process these subjects are going to be exposed to an experimental formulation that is untested and unproven. This could cause the individual to experience a hyper- or hypo-thyroid event, potentially jeopardizing their health. This is not a viable or sound option, and thus the use of athyrotic individuals in BE studies assessing levothyroxine sodium products should not be used and the current FDA recommendations of using euthyroid volunteers should continue to be the standard practice.

The current guidelines set forth by the FDA for assessment of therapeutic equivalence for orally administered products are time-tested, proven, and well-accepted by the industry. Mylan Laboratories fully supports and endorses these guidelines and does not believe that any of the changes endorsed by the endocrine societies should be implemented.

Product Quality Considerations

It has been well known throughout the pharmaceutical industry and the subject of several publications that levothyroxine sodium is a difficult product to manufacture and perhaps more difficult to maintain within approved specifications upon aging (i.e., long-term stability). The manufacturing process for levothyroxine sodium tablets utilized by Mylan includes the use of a potency factor to ensure that the drug product is formulated to contain 100% of label claim of Levothyroxine Sodium, USP. Since approval of Mylan's ANDA for Levothyroxine Sodium Tablets on June 5, 2002, through April of 2005, Mylan has released 160 batches of drug product which encompass all eleven product strengths approved in our ANDA. The content uniformity of the 160 batches has a mean of means of 100.7% with a range of RSDs from 0.7 to 3.3%. An evaluation of the content uniformity shows exceptional product homogeneity in that a relative standard deviation of 1.5% for a ten-tablet assessment is considered typical. Furthermore, the range of RSDs demonstrates that Mylan's product is consistent in uniformity from batch to batch. The nominal potency of these 160 batches is 99.7% with an average potency, independent of dose, ranging from 98.9% to 101.1%. A comparison of the potency test results with reference to the corresponding uniformity mean results generally show agreement within 1%. These data demonstrate that Mylan's generic Levothyroxine Sodium drug product does not exhibit variability amongst doses or between batch to batch (refer to Attachment B for data summary).

Of the 160 batches of Levothyroxine Sodium Tablets manufactured by Mylan through April 2005, 86 have been placed into the Mylan long-term stability monitoring program and 60 of these batches have been on stability for 12 months or longer. A review of these data (which includes both 18 and 24 months of test data at 25°C and 60% RH) supports product stability in that potency and dissolution remain well within approved specifications. These data indicate that Mylan's product formulation is chemically stable and retains its quality throughout its expiry (refer to Attachment C for data summary).

Proposal

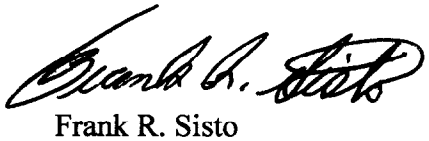
The significant body of data generated by Mylan demonstrates Mylan's ability to consistently produce a homogenous, potent and stable generic levothyroxine sodium tablet dosage form under a controlled manufacturing process. As these data prove that it is possible to consistently manufacture a high quality product with predictable potency and stability, Mylan would like to propose and support that Levothyroxine Sodium Tablets, USP be subject to more stringent assay (potency) specifications than the current and typical 90.0% to 110.0%. The drug product should be measured against assay specifications more in line with other drug products having a narrow therapeutic index. For example, Phenytoin, Carbamazepine, and Warfarin Sodium oral drug products are labeled with Assay requirements of 95.0% to 105.0% of label claim, 92% to 108.0% of label claim, and 95.0% to 105.0% of label claim, respectively.

Therefore, in the best interests of the consumer from a quality and safety perspective for this narrow therapeutic drug, Mylan proposes:

1) That the specification for product potency at time of release be between 95.0% to 105.0% of label claim, and

2) That the specification for product potency throughout the product's approved expiration dating period be between 93.0% to 107.0% of label claim.

Sincerely,



Frank R. Sisto
Vice President
Corporate Regulatory Affairs
Mylan Laboratories Inc.

Attachments

FRS/tlr

cc: Gary J. Buehler, Director
Office of Generic Drugs, CDER, FDA

David G. Orloff, MD, Director
Division of Metabolic and Endocrine Drug Products
CDER, FDA

Attachment A

Mylan Pharmaceuticals Inc.
Bioequivalence Study Summary of Baseline Corrected T4 Results

Sample Size of Study	Reference Brand Name	Single-dose Bioequivalence (2 x 300 mcg Tablets) Study									
		AUCt (mcg*hr/dL)¥				Cmax (mcg/dL)				Tmax (hr)	
		Mylan	Reference	Ratio†	90% CI§	Mylan	Reference	Ratio†	90% CI§	Mylan	Reference
29	Synthroid	163.0	150.9	108.6	102.9 - 114.6	6.01	5.66	105.5	100.6 - 110.6	2.84	2.57
23	Levoxyl	160.2	157.8	101.7	91.7 - 112.9	5.57	5.60	99.6	90.1 - 110.1	2.39	2.13
34	Unithroid	195.9	202.2	96.2	90.5 - 102.3	7.57	8.12	93.3	89.7 - 97.0	3.13	2.40

† = Ratio utilizing the log transformed parameters = (test value/ reference value) x 100
¥ = Area under the curve from 0 to 48 hours after dose administration
§ = 90% confidence interval from the log transformed parameter data

Attachment B

Mylan Pharmaceuticals Inc.
Levothyroxine Sodium Tablets, USP
Historical Record of Assay, Content Uniformity and Dissolution Data from Product Approval to May 2005

Strength (mcg)	#Lots	Assay 90.0% to 110.0%		Content Uniformity 85.0% to 115.0%; RSD NMT 6.0%				Dissolution NLT 70% (Q) in 45 minutes	
		Average	Range of Averages	Mean	Range of Means	RSD	Range of RSDs	Average	Range of Averages
25	13	100.2	95.8-102.9	101.2	97.8-104.2	1.6	0.9-2.9	86	81-92
50	23	100.0	97.3-103.2	101.0	98.3-104.6	1.5	0.8-2.3	86	79-94
75	18	99.4	97.7-104.2	101.1	99.2-104.4	1.5	0.8-2.1	84	76-93
88	12	98.9	96.1-101.6	100.2	96.8-102.4	1.5	0.7-3.2	85	79-96
100	25	99.1	96.8-102.5	100.2	98.2-103.7	1.5	0.7-2.7	85	77-96
112	13	99.0	96.1-102.1	100.3	97.3-103.2	1.4	0.9-2.2	87	80-95
125	15	100.1	97.6-104.6	100.6	98.1-104.5	1.6	1.0-2.3	86	77-91
150	12	99.7	94.4-103.3	100.4	95.7-102.4	1.4	09.-2.1	83	78-97
175	8	99.3	96.8-101.3	99.9	97.6-102.3	1.5	1.0-2.1	83	80-89
200	9	100.0	97.1-102.4	101.1	98.6-104.3	1.5	0.9-2.6	84	78-96
300	12	101.1	96.2-103.7	101.6	97.2-104.0	1.8	1.2-3.3	83	78-87
	Total 160								

Attachment C

Mylan Pharmaceuticals Inc.
Levothyroxine Sodium Tablets, USP
Stability Historical Record of Assay and Dissolution Data

Strength (mcg)	#Lots (Testing intervals NLT 12 months)	Assay Average 90.0% to 110.0%				Dissolution Average NLT 70% (Q) in 45 minutes			
		Initial	12 mo.	18 mo.	24 mo.	Initial	12 mo.	18 mo.	24 mo.
25	5	101.6	99.9	102.4	101.0	86	87	89	85
50	6	99.2	96.2	100.5	96.3	83	83	80	81
75	4	98.7	97.0	100.5	97.8	81	84	89	85
88	7	99.3	98.8	100.1	98.6	83	83	89	84
100	7	98.2	96.9	98.0	95.7	82	85	81	81
112	7	98.8	97.0	100.0	98.5	84	84	83	84
125	5	100.7	98.8	100.5	98.4	83	86	86	84
150	4	99.3	98.4	101.3	100.5	80	84	88	83
175	5	99.4	98.0	101.8	100.3	83	83	88	81
200	5	100.0	99.1	102.1	102.4	83	85	96	83
300	5	99.4	98.3	101.7	99.3	82	88	84	84