CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-411

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-411

Eli Lilly and Company
Attention: Gregory Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated October 11, 2001, received October 12, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Strattera® (atomoxetine hydrochloride) Capsules.

We acknowledge receipt of your submissions dated September 26, October 10, 18, 23 and 31; November 11, 12 and 20, 2002.

The September 26, 2002, submission constituted a complete response to our August 12, 2002 action letter.

This new drug application provides for the use of Strattera® (atomoxetine hydrochloride) Capsules for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) for children and adolescents ages 6 - 18 and adults.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the agreed upon enclosed labeling (text for the package insert and patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-411." Approval of this submission by FDA is not required before the labeling is used.

Post Marketing Commitments

We remind you of your post marketing study commitments in your submission of November 20, 2002. These commitments are listed below.

1. 75-day Repeated Dose Toxicity Study in Young Rats to qualify i(b)----------

   Study Start: April 14, 2003
   Final Report: November 15, 2003

2. Ames Test to qualify (b)----------

   Study Start: Estimated start date January 15, 2003
   Final Report: Estimated report date April 4, 2003

3. In vitro chromosomal aberration study to qualify i(b)----------

   Study Start: Estimated start date January 15, 2003
   Final Report: Estimated report date April 30, 2003

We also acknowledge your November 26, 2002, telephone commitment to conduct post marketing studies to assess long-term efficacy and effects on growth. We would like to promptly schedule a meeting with you to discuss the specific details of these studies and the timelines for their completion.

Please submit all clinical protocols to your IND for this product; and, all non-clinical and chemistry protocols and all final study reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), please include a status summary of each commitment in your annual report to this NDA. This status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, the number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled, 'Postmarketing Study Protocol', 'Postmarketing Study Final Report', or 'Postmarketing Study Correspondence'.

Chemistry Issues

1. A 24 month expiry is granted for drug product in commercial packages (30 count in 75 mL WHDPE bottles and 2000 count in 1500 mL WHDPE bottles) and physician sample packs (14 and 24 counts in 50 mL WHDPE bottles and 4, 10, 14 and 24 counts in blisters). A 12 month expiry is granted for the drug product physician sample packs of 4 and 10 counts in 50 mL WHDPE bottles based on the stability data provided.

2. We have not completed validation of the regulatory methods. However, we expect to continue to work with you to resolve any problems that may be identified.

Biopharmaceutics Issues

1. The following agreed upon dissolution method and specification has been approved for all strengths of atomoxetine HCl capsules (5,10, 18, 25, 40 and 60 mg) capsules:

Apparatus:	USP apparatus II (paddle) at 50 rpm
Medium:	1000 ml of 0.1 N HCL at 37°C
Specification:	Q = (b)--at 30 minutes.

2. Please note that we still do not consider atomoxetine hydrochloride to be a BCS class 1 drug since it fails to meet the criterion for dissolution.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, we request that you report any post-marketing cases of appendicitis or diabetes mellitus/hyperglycemia as 15-day reports.

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Regulatory Affairs Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Temple
11/26/02 04:22:36 PM

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APPLICATION NUMBER:

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APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-411

Eli Lilly and Company
Attention: Gregory Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated October 11, 2001, received October 12, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Strattera (atomoxetine hydrochloride) Capsules.

We acknowledge receipt of your amendments dated December 5 and 13, 2001; January 16, 18 and 31; February 11 and 27; March 25 and 28; April 11, 15, 18 and 30; May 8, 15, 22, 23, and 29; June 11 and 19; and July 16, 2002.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Clinical Issues

While we acknowledge that the data, in general, support the conclusion that there is no important QT prolongation at low plasma levels, those that would be seen in patients with normal CYP 2D6 metabolism and no inhibitor, there are data suggesting that at higher levels there may be an effect (primarily the data from the 75 mg BID PM group in Study LYAE; in addition, a subgrouping of patients, based on EM or PM status, from a pool of the phase 2-3 trials revealed a greater proportion of QTc outliers among the PM's compared to the EM's). Although we believe that no important effect on the QT interval was demonstrated at mean plasma levels at or below about 2000 ng/ml, there are relatively few data at or above these levels, and, as a result, we cannot reach a definitive decision at this time about whether there is or is not an effect of atomoxetine on the QT interval at these higher levels, and, if there is, what the plasma level threshold for such an effect might be. For this reason, you will need to prepare a comprehensive report in which you address the question of the relationship between higher levels of atomoxetine and the duration of the QT interval. Since atomoxetine will likely be used predominantly in the pediatric age group, it will be important to address this question in pediatric patients. If you believe you have in hand adequate data to address this question, they should be submitted. If you do not have sufficient data, you may need to perform additional studies. Our concern with the effects, if any, on the QT interval of higher plasma levels of atomoxetine arises because such

levels will be seen in the 8-10% of Caucasian patients who are poor metabolizers of CYP 2D6 as well as patients who take 2D6 inhibitors.

We would, of course, be happy to discuss with you appropriate approaches to addressing this question. In addition, it would be useful for you to attempt to estimate the proportion of patients who might be expected to achieve these higher plasma levels. The results of these additional analyses may or may not lead to a need for a description of the QT effects in labeling; for this reason, we are not proposing any labeling language pertaining to this issue at this time.

We also note that there is a paucity of long-term safety data in PMs in your database (13 PMs treated at a therapeutic dose for at least 6 months, and 1 such patient treated for at least 1 year). Please submit additional long-term safety data in these patients; long-term safety data in other patients expected to achieve the plasma levels achieved by PMs (e.g., EMs treated concomitantly with potent inhibitors of CYP2D6) would also be helpful.

Finally, we note that, although you have clearly established the short-term effectiveness of atomoxetine in children, adolescents, and adults with ADHD, you have no evidence of long-term effectiveness. The only submitted study of the effects of drug withdrawal showed no difference between atomoxetine and placebo. We will expect your commitment to pursue evidence of long-term effectiveness. In addition, the long-term effects of atomoxetine on growth have been assessed only in single arm studies. We would like to discuss possible longer-term controlled trials.

Labeling Issues

1. Accompanying this letter as an attachment is our proposal for the labeling of Strattera® Capsules. Please submit revised draft labeling identical in content to the enclosed labeling (text for the professional and patient package inserts). Explanations for our proposed changes are provided in the bracketed comments embedded within the proposed text. We would be available to discuss these proposed changes in more detail through a teleconference if you wish.

2. Although the draft label includes language pertaining to appendicitis, we are requesting that you report any post-marketing cases of appendicitis as 15-day reports.

Chemistry Issues

Establishment Inspections:

The Eli Lilly drug product packaging, labeling, and stability testing facility located in Indianapolis, IN (CFN #1819470) was found to be unacceptable by the FDA's Office of Compliance. We note that your application describes a second facility that performs these functions. If you plan to utilize the Indianapolis, IN site (CFN #1819470), a satisfactory inspection will be needed, otherwise the site should be withdrawn from the NDA.

Drug Substance Section:

1. Please provide the following data to support the two polymorphic forms of atomoxetine HCl:
   a) Information establishing that only two polymorphic forms of atomoxetine HCl (Form I and II) exist.
   b) Establish that the X-ray diffraction method selectively distinguishes between the two forms (I and II) of atomoxetine HCl. Provide data from the X-ray diffraction method demonstrating that the method can distinguish between the two forms of atomoxetine HCl.

2. Provide and include the impurity specifications for (used for the manufacture of atomoxetine HCl. Also, provide the analytical methodology used to measure optical rotation for the acceptance criteria of

3. Provide individual impurity acceptance criteria for PMAP specifications.

4. Include a specification for "Individual Unspecified Related Substance" and "Total Unspecified Related Substances" in the atomoxetine HCl drug substance specifications. Also, the term "Largest Unspecified Related Substance" in the drug substance specification is unclear and should be eliminated.

5. Include a specification for residual solvents including 1,3-dimethyl-2-imidazoline, toluene, ethyl acetate, tert-butyl methyl ether, 2-fluorotoluene and isopropanol in the atomoxetine HCl regulatory specifications, since these residual solvents are used in the manufacture of atomoxetine HCl. The specification should be reflective of the data from batches manufactured by the commercial process and consistent with ICH Q3C recommendations. Also, provide justification for the specification limit of 1,3-dimethyl-2-imidazoline.

6. Please lower the specification of Compound to NMT for the drug substance specifications. The specification for Compound should be reflective of the batch data from the batches which report the detection of compound below the quantitation limit of

7. For method B07447:
   a) Identify the impurity peak prior to A in the chromatogram on page 185, Vol. 1.4.
   b) Provide methodology that includes a 20 minute run time since large impurities I and K elute later
   in the run.

8. Methods B07447 for the assay and B07448 for the related substances appear identical except for the sample concentrations and the lengths of the run times. Please combine the two methods into one method for the assay and related substances with appropriate sample concentration and longer run time of 25 minutes and provide the validation data for the revised method.

__/__ page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Issues Common to Drug Substance and Drug Product

18. The stability protocols are unclear and confusing in their presentation. Submit clear revised stability protocols for both the drug substance and the drug product.

Drug Product Section:

19. The Indianapolis site (CFN #1819470) was not submitted to the NDA as a drug product manufacturer even though the 18 and 60 mg strengths were manufactured at this site. The drug product data from this site is, therefore, unacceptable. Submit this site to the NDA for FDA inspection as a drug product manufacturer or provide data for the 18 and 60 mg strengths from the commercial drug product site in Puerto Rico.

20. Provide information on any reprocessing operations used in the manufacture of atomoxetine capsules.

21. Provide a detailed sampling plan for the production batch analyses. The sampling plan should include details on the number of samples selected for analysis per batch and the location of the sample selected (e.g. beginning, middle, end).

22. Increase the run time for method B07251 for assay and content uniformity of atomoxetine capsules from 2 to 12 minutes to ensure inclusion of the potential impurities: ——— ——— at longer elution times.

23. Clarify whether the same response (in mV) can resolve ——— impurity from atomoxetine and other related substances for method B07252.

24. Include a specification for "Individual Unspecified Related Substance" and "Total Unspecified Related Substance" in the drug product specifications. The term "Largest Other Individual Related Substance" in the drug product specifications is unclear and should be eliminated.

25. Justify the specification of Compound ——— at NMT 0.5% in the drug product specifications.

26. Include the specification for water in the drug product specifications of atomoxetine HCl capsules. Also, provide a justification for not including microbial testing since water content increases up to approximately 10% on stability.

27. A ——— month expiration period for Strattera™ capsules is not supported. Provide updated stability data for all strengths of drug product batches manufactured at the commercial drug product site at Puerto Rico. The drug product batches should be manufactured utilizing the drug substance from the commercial drug substance manufacturer in Ireland.

28. Reduced testing for future stability drug product lots is unacceptable. Please perform testing at all time points for future stability lots. In addition, annual lots on stability should include one lot of each strength.

29. Incorporate specifications for water, S-enantiomer, Individual Unspecified Related Substances and Total Unspecified Related Substances and other regulatory specifications for the drug product stability protocol.

30. The expiration date for the physician sample packages of 4, 10, 14, and 24 count is also pending contingent on providing the stability data from the drug product manufactured at the Puerto Rico site utilizing the drug substance from the Ireland site.

Comments from the FDA Controlled Substances Staff

We have not yet determined whether or not we will recommend that atomoxetine be scheduled under the Controlled Substances Act (CSA); such a determination must await a full review of the results of Study LYBO by our Controlled Substances Staff (CSS). We have determined that the application may ultimately be approved, pending satisfactory resolution of the other issues discussed in this letter, before the CSS's review is complete. However, you must be aware that it is possible that a recommendation for scheduling under the CSA may be made, and, if the drug is scheduled under the CSA, this will need to be implemented after marketing.

Biopharmaceutics Issues

Dissolution Method and Specification
You are requested to adopt the following dissolution method and specification for all strengths of STRATTERA Capsules (5, 10, 18, 25, 40 and 60 mg):

Apparatus:	USP apparatus II (paddle) at 50 rpm
Medium:	1000 ml of 0.1 N HCL at 37°C
Specification:	NLT — at 30 minutes.

BCS Classification
Although atomoxetine hydrochloride is highly soluble and highly permeable, the slower release of the highest strength (60-mg) capsule in pH 6.8 buffer (<85% in 30 minutes) does not meet the criteria for being classified as a BCS Class 1 drug product.

Regulatory Status Update

Please provide any new information on the worldwide regulatory status of Strattera® Capsules for Attention Deficit Disorder, including the status of all actions either taken or pending before foreign regulatory authorities.

World Literature Update

Prior to the approval of Strattera®, we will require an updated report on the world archival literature pertaining to the safety of this product.

Safety Update

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

Post-Marketing Issues

While the following issues need not be resolved prior to approval, the following additional pre-clinical studies to qualify impurity will be required post-marketing:

1. We acknowledge your commitment to conduct a juvenile rat study to qualify impurity , as outlined in your submission of July 16, 2002. However, we recommend that a measure of motor activity be included in that study.

2. We request a commitment to perform an Ames Test and an in vitro chromosomal aberration study to qualify this impurity post-marketing. Athough in your submission of July 16, 2002, you argue that the impurity concentrations in the previously conducted studies were much greater than estimated human plasma levels, we do not consider this comparison to be valid.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Regulatory Affairs Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachments

25 page(s) of revised draft labeling has been redacted from this portion of the review.

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

/s/

Robert Temple
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