CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022075Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-075

Kyowa Pharmaceutical, Inc.
Attention: Lieselotte Bloss, DVM
Director, Regulatory Affairs
12 Carnegie Center, Suite 101
Princeton, NJ 08540

Dear Dr. Bloss:

Please refer to your new drug application(NDA) dated March 29, 2007, received April 25, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (istradefylline) tablets (b) (4) 20mg, and 40mg.

We acknowledge receipt of your submissions dated:

May 8, 2007	May 9, 2007	May 29, 2007	June 6, 2007
June 18, 2007	June 28, 2007	July 2, 2007	August 7, 2007
August 22, 2007	August 29, 2007	September 5, 2007	September 21, 2007
September 24, 2007	October 1, 2007	October 22, 2007	October 26, 2007\
November 9, 2007	November 14, 2007	December 20, 2007	January 22, 2008
January 30, 2008	January 31, 2008		

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

CLINICAL

We acknowledge that you have submitted three well-controlled studies (Studies 005, 006, and 013) that show effectiveness for the adjunctive use of istradefylline 20mg, 40mg, and 60mg/day (without clear evidence of dose response) in decreasing the percent of time awake spent in the OFF state in patients with advanced Parkinson's Disease (PD). Several other well-controlled studies of adequate size, however, do not show such an effect and in one of those studies, Study EU-007, an active control, entacapone, gave an almost significant result (p=0.06) while istradefylline showed essentially no effect. Entacapone, moreover, had a favorable effect on the PGI, a patient-rated global measure in that study, while istradefylline did not. These findings, taken together, establish effectiveness in decreasing OFF time, but raise questions about the strength of the finding.

A more important problem, raising the critical question of what patients should receive istradefylline, is raised by the uniform failure of the trials to find any other result that supports the clinical utility of istradefylline or suggests meaningful benefit to patients. There are no nominally significant between-treatment contrasts favoring istradefylline compared to placebo on any secondary outcomes in any of the trials, including those assessing other symptoms of PD (e.g., UPDRS, ON time) or global measures of functioning (e.g., CGI, SF-36). These results are conspicuous, compared to all other recently approved treatments for advanced PD, for the absolute lack of demonstrable effect on these other measures. We acknowledge that there is no requirement under law that a new drug be as good as other available treatments, but any inferiority should not represent a risk to patients. It could perhaps be argued that these other treatments provide only symptomatic benefits, and that, substituting an "inferior" treatment would pose no important harm to patients, but we do not agree with this view. Parkinson's Disease is a serious disease, and effective symptomatic treatment can prevent serious clinical outcomes (e.g., falls), even if the treatment has no effect on the underlying progression of the illness, and inferior performance with respect to these other endpoints represents real risk. Although we recognize that the comparative observation that all other recently approved treatments for advanced PD show advantages compared to placebo on signs and symptoms other than OFF time whereas yours does not is based on cross-study comparisons, which are typically unreliable, in this case, we believe that the totality of the evidence justifies our concerns. In addition, in Study EU-007, the one study that included an active comparator (entacapone), entacapone showed an effect on the PGI, while istradefylline did not. Admittedly, of course, this was a study that showed no effect of istradefylline on OFF time. The lack of effect on the disease is further supported by the lack of a statistically significant change in UPDRS, CGS, and PGI scores in the double-blind, placebo controlled study (Study 051) examining istradefylline 40mg as monotherapy in Parkinson's disease.

It is possible, we suppose, that this class of compounds, in contrast to dopaminergic agents, has a very specific effect in patients with PD, and improves OFF time with no effect on any other PD symptoms, but this does not help identify a population that should be given istradefylline, rather than other available treatments that improve not only OFF time, but other symptoms as well. Further, even if this "specific-effect" hypothesis were somehow true, we would still expect that any important effects on OFF time would translate into an improvement on non-specific global and/or quality of life measures, especially those measures that are rated by patients. The complete lack of such improvement across multiple studies and measures suggests either that the effect seen on OFF time is inconsistent or clinically trivial, and/or that some effects of the drug are sufficiently distressing to cause patients' overall judgments to be that no benefit was obtained.

These data, then, taken as a whole, lead us to conclude that there appears to be no population for whom istradefylline would be a suitable choice, and, therefore, we cannot support its approval at this time. However, we do believe that it might be possible that, with additional data, approval of the application could be supported.

Specifically, if you were to demonstrate, in an adequately designed and conducted controlled trial, that patients with advanced PD, who had been explicitly maximally and optimally treated with all appropriate available treatments, had a decrease in OFF time on istradefylline compared to placebo, this might support approval of the application, as the gain in OFF time would not be obtained at the expense of other benefits. We, of course, would be happy to work with you to design such a study.

CLINICAL PHARMACOLOGY

If you wish to pursue approval in the future we would like to inform you that the following Phase 4 commitments would be required:

1. A drug interaction study to investigate the inhibition potential of istradefylline on Pgp.

2. In vitro studies to explore the induction potential of istradefylline on CYP1A2. If there is such a potential, an in vivo study may be necessary.

NONCLINICAL

Mineralization in the brain was first detected in the 2-year carcinogenicity study in the rat. As requested by the Agency (cf. minutes of End-of-Phase 2 Meeting, September 23, 2003), you re-examined brains from other toxicity studies in rat and dog and from the 2-year carcinogenicity study in mouse. For the 4-, 13-, and 26-week studies in rat and the 2-year mouse study, your re-examination of brain included cutting additional sections and employing a variety of stains (e.g., PAS, von Kossa, alizarin red). Using these techniques, you detected a dose-related incidence of foci of mineralization in brains in the 13- and 26-week rat studies, but not in the 2-year mouse study. It is not clear that similar techniques were used to re-examine brains from the subchronic and chronic toxicity studies in dog.

You provided no overall summary of the methodology used and the results of the original and re-examination of brain samples, or expert opinions regarding the nature of the mineralization and possible relationship or lack of relationship to drug. This omission was particularly problematic since data relevant to the finding of brain mineralization were located in numerous individual reports in various files throughout your electronic submission. None of the electronic files was identified by study title, only by study number. This made finding relevant studies (and overall review of the NDA) unnecessarily burdensome, particularly since many of the pivotal studies had more than one identifying number and related studies were not always cross-referenced.

In order for us to complete our evaluation of the brain mineralization finding, you will need to provide an overall summary as described. If an expanded histopathology of brain was not conducted for dog as was done in the rat and mouse, it should be conducted and the results submitted for review.

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 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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), you may request a meeting or telephone conference with this division to discuss what 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 this application is approved.

If you have any questions, contact Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation 1
Center of Drug Evaluation and Research

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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