EGILMAN'S EXHIBIT 1

[redacted]

Memorandum Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

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FROM: Paul Leber, M.D.
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HFD-120

SUBJECT: NDA 20-592 Zyprexa® [olanzapine]

TO: File NDA 20-592
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my endorsement of the review team's unanimous recommendation that the NDA for Zyprexa be declared **approvable.**

Introduction

The review team's exposition of the evidence documents that the sponsor's application provides sufficient information to establish, within the meaning of the Act, that olanzapine will be "effective in use" and "safe for use" under the conditions of use recommended in the labeling developed by the Division's review team. In the course of its systematic review of the information and reports provided, the Review team uncovered no finding or issue that could be considered exceptional, disconcerting, or controversial. Accordingly, the NDA has not been presented to the Psychopharmacologic Drug Products Advisory Committee.

Our understanding of the data adduced in the 4 clinical studies deemed by design capable of providing evidence of Zyprexa's effectiveness in use was increased substantially by the analyses conceived of and executed by Dr. Hoberman, the mathematical biostatistician assigned to the review team. His innovative conceptualization of "dropout cohorts" that provide a visual display of the status of dropout's by treatment during each interval over the course of a randomized trial provides an evidence rich basis to assess the impact of censoring on analyses of the " intent to treat" samples upon which primary descriptions of clinical trial results ordinarily rest.

Incidentally, my singling out of Dr. Hoberman's work is in no way intended to

diminish the caliber of work done by other members of the review team. The team's workup was outstanding.

In sum, although I have no reservations about the regulatory decision being recommended to the Office, I do have a number of observations about olanzapine and the sponsor's development program that are of potential importance in regard to the kind of promotional claims that it may or may not be appropriate to allow Lilly to advance for Zyprexa.

Effectiveness (absolute and relative?)

The NDA provides "substantial evidence" that olanzapine is an effective antipsychotic drug product. This conclusion, however, is not intended to convey a judgment that the sponsor's development program has evaluated every important aspect of olanzapine's use in the treatment of psychosis that the agency might like to have available at the time an NDA is approved, or that a prescribing physician would prefer to possess.

The evidence adduced in the sponsor's short term (nominally 6 week long) studies, although it unquestionably provides compelling proof in principle of olanzapine's acute antipsychotic action, does not, because of 1) the highly selected nature of the patients admitted to study, 2) the high incidence of censored observations in the controlled trials, and 3) the indirect means used to assess the product's antipsychotic effects, provide a useful quantitative estimate of how effective[1] (even in the short run) olanzapine actually will be in the population for whom it is likely to be prescribed upon marketing.

The relatively short duration of the controlled clinical trials the sponsor relies upon, as might be anticipated, leaves us largely uninformed both about how effective a "maintenance" treatment olanzapine will be in extended use,

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[1] This acknowledgment is not an implication that some other information gathering strategy on drug performance/use can accomplish what randomized controlled trials of the sort now conducted in commercial drug development cannot. To the contrary, those who use the limitations of the RCT to promote the fatuous notion that observational outcome studies can provide insights that the RCT cannot are deluding themselves. It is a fact that the typical RCT's we rely upon have limited external validity, and that is weakness. It is one, however, that pales in comparison to those of outcome "studies" that have, as a result of their uncontrolled comparisons and limitless undeclared assumptions, neither internal nor external validity.

and how best to administer it (i.e,. dose and regimen) for that use.

These limitations, of course, are hardly unique to the set of trials conducted by Lilly in its development of olanzapine. In fact, as development programs go, Lilly's evaluation of olanzapine is a reasonably good one in light of its primary intent.

Commercial drug development programs are intended to adduce, in the shortest interval possible, the evidence that will allow the approval of an NDA. Accordingly, sponsors do not ordinarily attempt to provide answers in their NDA submissions to every question that may arguably provide useful information about their product.

Moreover, it is not only economic considerations, but the prevailing political environment, one which places great weight on the pace of drug development (i.e., achieving the shortest possible latency between drug discovery and drug availability at the bedside), that undermines the incentive to approach the development of a new drug with the kind of flexibility that allows for the adjustment of development plans to address questions and issues that were unanticipated at the start of a development program (e.g., issues identified during clinical testing)

There is, however, a force at work that operates to increase the volume of clinical testing: marketplace competition. This characteristic of the current health care economy virtually compels those developing new drugs, in particular those that will compete with already marketed products, to advance claims of superiority or advantage. It is this need that drives the conduct of comparative drug trials.

One aspect of this is quite paradoxical. In the midst of an epoch where much attention is being given to efforts to make both the drug development and approval process more efficient (i.e., to reduce the number of studies that, respectively, must be submitted and reviewed, to support NDA approval), sponsors are being driven to conduct more studies and, to boot, ones that are more complicated and difficult to conduct, at least validly. I write, of course, of studies intended to show a product's advantage to an already marketed drug.

Such studies are not only more difficult to design and conduct fairly, but are also more difficult to interpret. Indeed, their assessment requires that attention be given to a number of issues that the "proof of principle"

randomized, controlled effectiveness trials that regulators have long been accustomed to evaluating for assessing effectiveness do not pose.

The typical controlled trial intended to document the advantage of a new drug usually involves some kind of comparison between the new drug and an already marketed product, typically one that dominates the market. Haloperidol, for example, is, if such a thing exists, pretty much the "standard" antipsychotic drug product; accordingly, it is the product against which new antipsychotic products are typically compared. Incidentally, these comparisons need not be performed only in "stand alone" comparison studies, but are often 'piggy-backed" onto the design of the more traditional effectiveness trial.

The review of NDAs, as a consequence, no longer focuses entirely on the relatively simple issue of whether or not the product is, within the meaning of the Act, "effective in use " and "safe for use," but on the much more vexing, perhaps unanswerable question, of whether or not the new drug is better than the standard, if not globally, then on some clinically important domain (ease of use, freedom from one or more untoward effects, etc.).

None of this is wrong, in principle. The comparative performance of a new drug is not only a legitimate question, but an important one. Who would not want to know which of several competing products is most effective and most safe? Who would not want to know that a particular drug, all things considered, gives a "bigger bang for the buck.?" The problem, of course, is that mere wanting is not sufficient. Valid comparisons of drug performance are not readily obtained. Moreover, even comparisons that on face appear compelling and reasonable can prove misleading.

A primary reason is that the information required to determine whether or not a particular comparison is fair and valid is rarely available[2].

[2] This is an assertion. There are, as yet, no regulatory standards vis a vis comparative claims. I believe, however, that for a drug product comparison to be meaningful, the products involved must be compared at equi-effective doses under conditions that do not give one product an unfair advantage. I also believe that, because equi-effective doses may not be the same from sample to sample, that a valid comparative design must be able to show, from its internal results (not historical expectations), that the drugs compared are being administered at the an equivalent position along their response vs dose curve.

Another problem is that clinical studies, whether conducted by academicians or commercial corporations rarely, if ever, provide a valid estimate of the "effect size" of a product even when the estimate derives from the result of a clinical trial executed with care and competence. If one cannot know reliably what the effect size is, how can one judge the clinical importance of differences in the size of the effect measured among several products?

Moreover, one cannot always be confident as to what an observed between treatment difference adduced on an instrument is due. This concern reflects the oft ignored fact that validity cannot be ascribed to a rating scale in isolation, but to the use for which that scale is employed.[3]

These observations about the problems of comparative inference are not put forward solely for academic reasons. The fact that differences found in clinical trials comparing products have arguable external validity is of major regulatory importance vis a vis drug product labeling and advertising.

Given this background, I will explain why I believe the data adduced in the Zyprexa NDA is, although readily able to support the NDAs approval, insufficient to permit the sponsor to make claims asserting the product's superiority to haloperidol.

In study **HGAD**, a 23 center, study involving some 335 patients randomized to 3 dose ranges of olanzapine (5 +/- 2.5 mg/d, 10 +/- 2.5 mg/d, and 15 +/- 2.5 mg/d), haloperidol (15 +/- 5 mg/d) and placebo, there are no clear findings

[3] The point made is that the validity of a test cannot be assessed without considering the use to which the test is put. A difference in outcome between drug and placebo assigned patients detected using a multi-item rating instrument may validly reflect a therapeutic effect the instrument was designed to measure. A difference found between two pharmacologically active drugs on the same assessment instrument, however, may not reliably speak to the differential effectiveness of the two products, but to some other consequence of drug action that is detected by the test instrument. The Hamilton Scale for Depression, for example, is sensitive to changes induced by established anti-depressants that have nothing to do with either drug product's therapeutic antidepressant action. Accordingly, caution is required in interpreting the meaning of between treatment differences even when they are detected using instruments that are widely accepted as "valid" for what may seem to be a very closely related use.

that can be claimed to show that olanzapine is more effective than haloperidol, although there are certainly some differences that could be described as "hints" of it. These hints, however, although they are consistent with common expectations predicted by the pharmacology of the two drugs[4] must also be considered in light of the patient sample's prior experience with haloperidol and the doses at which the products are compared. In sum, I would not interpret the results of HGAD as support for a comparative claim, either explicit or implied, because 1) its design is inappropriate,and 2) the sample of patients used is an inappropriate choice.

E003, is a basically failed study; moreover, by design and patient sample selection would, if positive, not prove what the sponsor's wants to show.

Study HGAJ, Lilly's very large[5] randomized trial comparing outcomes over a 6 week period among schizophrenic patients treated with olanzapine and haloperidol (the dose of each drug was permitted to range between 5 mg and 20 mg a day, being adjusted according to the clinical judgment of prescribers) is the second source that the sponsor can argue shows an advantage of olanzapine. The titration design of **HGAJ** makes it ill-suited for evaluating the comparative performance of two drugs, however. Moreover, like other studies in the sponsor's development program, it suffers in that it entered a sample of patients with a history of prior use of haloperidol, a factor, as noted earlier, that makes the study sample inappropriate for comparison purposes.

I am not, however, as concerned as Dr. Laughren is about what he characterizes as the small magnitude of the estimated between treatment difference, nor that fact that a very large study was required to show that the observed difference is unlikely to be due to chance.

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[4] Both the comparative neurotransmitter receptor binding profiles of the products and the electrophysiologic studies of the products would lead many experts to predict that olanzapine would be expected to exhibit less 'neuroleptic' activity than haloperidol. This, in turn, would not only be expected to influence the incidence and kind of ADRs reported, but any effectiveness instruments that are sensitive to the subset of psychotic phenomena (e.g., so-called negative signs/symptoms of Schizophrenia) that overlap with those of pseudoparkinsonism.

[5] 1950 or so subjects in 186 US and European centers: 1312 on randomized to olanzapine, 636 to placebo

The size of a drug's effect is, as my earlier comments indicate, an abstraction, a notion that is not yet fully reified. Importantly, the agency, wisely given the potential difficulties involved in reifying the concept, has steered clear of the issue. I believe we should do so in the arguments about HGAJ.

The allegedly "small" size of the measured difference, in my view, is not its fault, at least from a regulatory perspective. In fact, if I were convinced that differences observed in a study were truly a valid and accurate reflection of a real difference in therapeutic effectiveness of the products compared, I would willingly endorse the presentation of the evidence supporting the conclusion in product labeling, although, as a matter of truth in labeling, I would, if such hypothetical evidence did exist, require the sponsor to include a display of the empirical cumulative distribution of the between product difference in product labeling.

In sum, although I have no reservations at all about concluding, from the evidence adduced and reported, that olanzapine will be effective in use within the meaning of the Act, I would not go further.

Moreover, I believe it is proper to ask that the firm make a commitment to conduct clinical trials that can evaluate in a valid and meaningful manner Zyprexa's performance in extended use as a maintenance treatment.

Evidence of safety for use

Preclinical findings

The full panoply of preclinical tests required to support the approval of an NDA have been performed and reported. Review of the reports submitted has not detected any result that would preclude approval of the NDA, although some findings (e.g., those involving results of in vivo lifetime carcinogenicity testing) warrant description in product labeling.

Clinical findings

No pharmacologically active drug substance is absolutely free of risk. This caveat offered, the evidence adduced in clinical testing that has so far been reported to the Zyprexa NDA is more than sufficient to support the conclusion that olanzapine, within the meaning of the Act, is safe for use under the

directions of use given in the Division's draft labeling.

It bears note that this conclusion is strongly conditioned on the evidence so far adduced. No one should be surprised if, upon marketing, events of all kinds and severity not previously identified are reported in association with olanzapine's use. Moreover, post-marketing experience may easily provide a very different impression of what are or are not the primary considerations of importance to the clinician and patient who, respectively, use and take, Zyprexa. Again, these statements reflect a generic limitation on regulatory inferences of 'safety in use' that derive from limited clinical experience with samples of patients who do not fully reflect the population likely to be treated with a drug upon its approval.

The safety data base reported upon in the Zyprexa NDA, at the time this approvable action is being contemplated, involves approximately 2500 patients. While this is far above the minimum experience required for NDA approval, it is not as robust as it may appear, especially if Zyprexa proves to be, upon marketing, a very popular drug product. Under such conditions, a very low probability of risk, one too small to make it likely that we would see even one case of the event in the NDA, might be sufficient to generate substantial numbers of cases of the event upon marketing.

On the other hand, there are risks that seem certain to be realized; fortunately, they are not likely to be very different from those associated with other antipsychotic drug products that have a similar profile of receptor binding.

Olanzapine's dopamine receptor antagonist actions make it likely that the product will cause prolactin elevation, pseudoparkinsonian signs and symptoms, tardive dyskinesia and the neuroleptic malignant syndrome. It's potent anticholinergic activity may cause some distress and its relatively potent alpha adrenergic antagonism probably will be associated with orthostatic hypotension, syncope, and risks that can arise as a secondary consequence of these latter events.

In any event, the labeling text as proposed alerts the prescriber to these risks. If adopted as proposed and/or recommended (the sponsor still has work to do), the Zyprexa product labeling will be informative and not false or misleading in any particular.

Recommendation:

Issue the draft approvable action letter that is forwarded in the company of this memorandum and action package.

Paul Leber, M.D.
8/18/96