CENTER FOR DRUG EVALUATION AND RESEARCH

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OFFICE DIRECTOR MEMO

Office of Drug Evaluation-I: Decisional Memo

Date	August 30, 2012
From	Ellis F. Unger, M.D. Director Office of Drug Evaluation-I Office of New Drugs CDER
Subject	Office Director Decisional Memo
NDA #	**NDA 203109 and sNDA 21845/S-008 (TSI #1311)**
Applicant Name	Pfizer, Inc.
Date of Submission	November 30, 2011
PDUFA Goal Date (post 3-month extension for major amendment)	August 30, 2012
Proprietary Name/ Established (USAN) Name	Revatio (sildenafil)
Dosage Forms/ Strengths	Tablet 20 mg, Injection 10 mg, Powder for Oral Suspension 10 mg/mL
Indication	Treatment of pulmonary arterial hypertension
Action:	Approval, with Post-Marketing Commitment

This memorandum summarizes the rationale behind my decision to revise the labeling for Revatio and to require that the manufacturer of Revatio (Pfizer) evaluate Revatio's effect on the risk of death in adult patients with PAH.

The clinical data have been well-described by the review team, including Drs. Brar (clinical pharmacology), Gordon (clinical), Lawrence (statistical), Karkowsky (cross-discipline team leader), Southworth (Deputy Director for Safety), and Stockbridge (Division Director), and will be summarized here only briefly.

Sildenafil is a phosphodiesterase type-5 inhibitor indicated for the treatment of PAH (WHO Group I) in adults, to improve exercise ability and delay clinical worsening. These claims were based on short-term (12- to 16-week) studies.

The pediatric development program included study A1481131 (#31), a 16-week, phase 3, placebo-controlled, dose-ranging study in patients 1 to 17 years of age. A second study (A1481156, #56) was a long-term randomized extension of study #31.

In Study #31, pediatric subjects (n=234) with PAH (1/3 primary; 2/3 with PAH 2° to congenital vascular abnormalities) were stratified by age group and randomized to placebo or one of 3 weight-adjusted sildenafil dosing tiers. The tiers were selected to match exposure in the pediatric population to low, medium, and high doses in adults. The 1° efficacy endpoint was the percent change in peak VO_2 (normalized to body mass) at trough plasma levels, from baseline to Week 16, assessed by cardiopulmonary exercise test (cycle ergometry), for those who were able to cooperate. Secondary endpoints included pulmonary vascular resistance index (PVRI), assessed invasively by right heart catheterization, as well as WHO PH functional class, respiratory exchange ratio and time to peak VO_2, and physical and psychosocial scales from the Child Health Questionnaire.

Study #56 was a long-term extension study wherein subjects originally randomized to placebo in Study #31 were re-randomized to one of the 3 dosing tiers. Once all subjects completed the Week 16 assessments in Study #31, the blind was broken and investigators could titrate sildenafil doses as clinically indicated.

The pVO_2 endpoint was analyzed using last observation carried forward (LOCF). pVO_2 in the pooled sildenafil groups showed an increase of approximately 10% relative to baseline, and relative to the placebo group (there was minimal change in the placebo group), but the treatment effect was not statistically significant (p=0.056). For all sildenafil groups combined, there was a modest decrease in PVRI (-4.1 Woods units/m^2, 95% confidence interval (CI) -8.0 to -0.2, p=0.04). When corrected for baseline, there was an apparent dose-response in the reduction in PVRI. The statistical reviewer removed 4 outliers that mostly favored the sildenafil group; not surprisingly, the results were no longer statistically significant when these data were removed. There was no correlation whatsoever (R^2=0.05) between Δ PVO_2 and Δ PVRI, although, as noted by Dr. Stockbridge in his memo, these parameters have not correlated well across studies of PAH drugs in adults.

The major finding was a dose-related decrease in survival. There were no deaths in the 16-week study (#31), but 35 deaths in the extension study (#56). There were 5, 10, and 20 deaths in the low-, middle-, and high-dose tiers, respectively. PAH is a serious disease with high mortality, and causes of death were typical for the patient population. Given that survival was not a planned study endpoint, all analyses on mortality are *post hoc*.

An analysis of mortality according to sildenafil dose at the time of event (or time of censoring) would be highly biased, given that sildenafil doses could be increased as clinically indicated. (Patients who were doing poorly would more likely have had their doses increased.) Thus, the most reasonable analysis here is an intent-to-treat analysis, based on the assigned dose at the time of randomization.

As noted in the statistical review, using a proportional hazards model stratified by weight class and assuming a linear dose-response, the estimated hazard ratio (HR) for mortality comparing the middle- and low-dose strata is 1.89; 95% CI 1.18, 3.03; p=0.008. Because of the assumption of linearity, the HR is the same for the comparison between the high- and middle-dose strata. The estimated HR for the comparison between the high- and low-dose strata is ~3.6. If linearity is not assumed, then the HR for mortality comparing the middle- and low-dose strata is ~2.0 (p=NS). For the comparison between the high- and middle-dose strata, the HR is also ~2.0 (and p=NS). The estimated HR for the comparison between the high- and low-dose strata is 3.5; p=0.015.

The review team expended considerable effort in their quest to better understand the mortality findings. They found no patterns in the discontinuations, serious adverse events, common adverse events, laboratory findings, EKG findings, or vital signs to support an underlying mechanism that would explain a dose-related decrease in survival.

Most of the review team found the evidence of harm to be reasonably compelling, and some considered the evidence to be very concerning. Dr. Brar and his colleges were an exception. The pharmacometrics team acknowledged the seriousness of the mortality finding, but noted several inconsistencies that seemed to undercut the persuasiveness of the signal. Dr. Stockbridge was also less certain, and found "…the evidence that sildenafil is harmful is…weak." He concluded that "The net result cannot be a recommendation for the use of sildenafil in children, but neither do I believe these data strongly impugn use in children and even less do they impugn long-term use in adults–where there is a disease progression claim." In terms of the need for a Post-Marketing Requirement for evaluation of long-term safety in adults, Dr. Stockbridge noted: "I do not believe the findings in the pediatric program are sufficiently likely to represent a true mortality signal to warrant such a study in adults." On these

points, I respectfully disagree; although the feasibility of a Post-Marketing Requirement for evaluation of long-term safety in adults is another matter (see below).

There are a number of considerations with respect to the *post hoc* finding of dose-related mortality.

1. Is dose-related mortality a true positive finding, or is it a false positive finding?

There are generally 2 factors that contribute to false positive findings: bias and play of chance.

a. Bias

Bias is always a concern in experimental medicine. Adequate and well-controlled studies utilize randomization, blinding, and pre-planned statistical plans, among other strategies, to reduce or largely eliminate the influence of bias. With respect to the findings here, we know that death is a "hard" endpoint that is not susceptible to bias. Moreover, had bias been operational in this study, it would have influenced the results in the opposite direction – toward enhanced survival with higher sildenafil dose. Thus, it can be said with reasonable certainty that the mortality findings are not the result of bias.

b. Play of chance

Play of chance can take many forms. Unfavorable randomization can lead to imbalances in baseline characteristics that favor one treatment group or another. Similarly, differences in concomitant therapies between experimental groups can influence study results. We acknowledge, of course, that even when all characteristics among treatment groups are seemingly indistinguishable, a statistically significant difference can occur by chance alone, i.e., Type-I error.

For the present study, the statistical persuasiveness of the findings has been estimated by various techniques. As above, Dr. Lawrence estimates p-values in the range from 0.015 to 0.008. Dr. Karkowsky puts the risk between 1 in 67 (high- vs. low-dose) and 1 in 125 (assuming a dose-response model).

It is important to note, however, that these estimates are based on 2 independent pairwise comparisons. The HR for mortality comparing the high-and medium-dose groups is ~2, and the HR for mortality comparing the medium- and low-dose groups is ~2.

In order to consider the probability of a result this extreme arising by chance, I ran a simulation as follows:

There are 3 treatment groups (high-, medium-, and low-dose) where the total n=229, and the n's for the respective groups are 100, 74, and 55. Within this set of 229 subjects, we distribute 35 events (there were 35 deaths overall) in random fashion, where H, M, and L represent the numbers of events in the high-, medium-, and low-dose groups, respectively.

Given that H + M + L = 35, the salient question is the frequency that:

1) (H/100) / (M/74) >= 2

and

2) (M/74) / (L/55) >= 2

Out of 120,120 simulations, this occurred 6 times, a rate of 0.00005 or 1 in 20,000. (Our usual standard for a false positive finding is 1 in 20, i.e., $p<0.05$.)

Like Dr. Stockbridge, I would be more confident about causality if some type of important dose-related toxicity had been evident, e.g., arrhythmias, serious infections, etc. Such data could have provided a mechanistic underpinning to support the effect.

But experience has shown that some drugs with salutary pharmacodynamic effects in the short term have been deleterious in the long term. There are several examples in the cardiovascular arena, the most famous of which is CAST. There are also examples of drugs for left heart failure (amrinone, for example, a phosphodiesterase III inhibitor) that fit this picture.

The uncertainty about causality aside, there are two hypothetical scenarios that provide some insight here. First, if we were considering these data as a way to support efficacy and safety in a pediatric population but had no data in the adult population, we would not grant approval for this drug. Second, if the mortality results had been the same, but the data from the high- and low-dose groups had been reversed, we would have given serious consideration to granting a mortality claim. It would be irresponsible, therefore, not to take these mortality findings seriously, especially because we can categorically rule out the influence of bias here.

If we are willing to accept the likelihood that sildenafil is causally related to mortality at the doses studied and in the population studied, the next question, *a critical question*, is the generalizability to the adult PAH population.

In the short term, there were no deaths in the pediatric studies. We have no long-term data in adults. Thus, based on available data, there is simply no way of knowing whether the reason the signal for dose-related mortality has not been observed in adults is because adults are just inherently different from children (or PAH is inherently *different* in children), or whether long-term studies in adults would, in fact, show dose-related mortality.

In light of the above, we are taking the following actions today:

1. We are approving an oral suspension for adults who are unable to swallow a pill. See approval letter and reviews.
2. Labeling will be revised to include the design and results of Studies #31 and #56 in section 8.4 under “Pediatric Use.” A Kaplan-Meier Plot of mortality by REVATIO dose will be shown.
3. The indications section of the label will be revised to note that REVATIO is indicated for the treatment of PAH in adults to improve exercise ability and delay clinical worsening, and that the studies that established effectiveness were short-term (12 to 16 weeks)
4. Under “Warnings and Precautions,” a new warning will be added in the first position, i.e., 5.1, stating that use of REVATIO, particularly chronic use, is not recommended

in children. The warning implies that use in children can still be considered (i.e., there is no contraindication), and that chronic use poses a particular risk for children, consistent with the findings in the trials:

> Mortality with Pediatric Use, "In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children *[see Use in Specific Populations (8.4)]*."

5. My belief is that a Post-Marketing Commitment is appropriate for adult patients with PAH, and the approval letter will describe that requirement. There are issues regarding the feasibility of conducting such a trial, and we have been in discussions with the applicant. Given that the issue of long-term safety is germane to other treatments for PAH, we may consider taking the issue to an advisory committee for public input and comment.

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/s/

ELLIS F UNGER
08/30/2012