DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for

The purpose of this letter is to notify you that after carefully considering the recommendations of the Endocrinologic and Metabolic Drugs Advisory Committee on July 1 and 2, 2008, and other available data and information, the Division of Metabolism and Endocrinology Products has determined that additional evidence will be needed for your product to address concerns about cardiovascular risk.

Reliance on HbA1c remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication to treat hyperglycemia secondary to diabetes mellitus because improved glycemic control has immediate clinical benefits and also has long-term benefits on microvascular complications. However, diabetes mellitus is associated with elevated risk of cardiovascular disease, which is the leading cause of morbidity and mortality in this patient population, and it is important to provide reassurance that a new treatment does not increase this risk to an unacceptable extent. To establish the safety of your new anti-diabetic drug to treat type 2 diabetes based on HbA1c measurements, you must demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk.

Therefore, we expect the development program for your type 2 diabetes product to include the following:

- A meta-analysis should be performed of important cardiovascular events across phase 2 and 3 controlled clinical trials. These events would always include cardiovascular mortality, myocardial infarction, and stroke and could include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and 3 programs

should include patients at higher risk of cardiovascular events, such as those with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. As these types of patients are likely to be treated with your anti-diabetic agent, if approved, this will also represent a population more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety. You should ensure that phase 2 and 3 clinical trials are appropriately designed and conducted so that a valid meta-analysis can be performed. You should also provide a protocol describing the statistical methods for the proposed meta-analysis, including the endpoints that will be assessed. At this time, we believe it would be reasonable to pool placebo-controlled trials, add-on trials (drug vs. placebo, each added to standard therapy), and active-controlled trials. It is likely that the controlled trials will need to last more than the typical 3 to 6 months duration to obtain enough events and to provide data on longer-term cardiovascular risk for these chronically used therapies.

- You should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, the cardiovascular events described above during all phase 2 and 3 trials.

- Prior to approval, you should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of important cardiovascular events occurring with the control group and show that the upper bound of the 2-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8. This can be accomplished using the integrated analysis of the phase 2 and 3 clinical trials described above. If the integrated analysis approach will not by itself be able to show that the upper bound of the 2-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8 then a single, large safety trial should be conducted that alone, or added to other trials, would be able to satisfy this upper bound. Regardless of the method used, we would also be interested in the rest of the confidence interval and the point estimate of the risk increase. For example, it would not be reassuring to find a point estimate of 1.5 (a nominally significant increase) even if the 95 percent upper bound was less than 1.8.

- If the premarket application contains clinical data that show that the upper bound of the 2-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3 and the overall risk-benefit analysis supports approval, a postapproval cardiovascular trial may not be required.

- If the premarket application contains clinical data that show that the upper bound of the 2-sided 95 percent confidence interval for the estimated risk ratio is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarket study will be needed to definitively show that the upper bound of the 2-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. This may be achieved by combining the results from a preapproval safety study with a similarly designed postapproval safety study.

You are encouraged to discuss with the Division your plans for addressing cardiovascular risk and we strongly recommend you submit your proposed plan for review before you implement it.

If you have any questions, contact Lina AlJuburi, Pharm.D., M.S., Chief, Regulatory Project Management Staff, at (301) 796-1168.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research