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APPLICATION NUMBER:
202293Orig1s000

OTHER ACTION LETTERS



NDA 202293

COMPLETE RESPONSE

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated December 27, 2010, received December 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

We acknowledge receipt of your amendments dated January 5, 12, 27, 28, and 31, February 1 and 16, March 23 and 30, April 11, 12, 13, 14, 22, and 28, May 9, 13, 16, 18, 20 (2), 23, and 24, June 2 (2), 3 (2), 10, 13, 14, 16, 17, 22, 24, and 30, July 13 and 22, August 1, 12, 17, 22 (2), 25, 26, and 30, September 1, 2, 7, 9, 14, 19, 20, and 22, October 18, 20, and 27, November 2, 8, 10 (2), 11, 15, 16, and 21, and December 2, 6, 7, 12, 19, and 29, 2011, and January 9 and 10, 2012.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. Cancer

Two 2-year studies in rats and mice did not identify a carcinogenic response for dapagliflozin. However, there were numeric imbalances for breast and bladder cancer in your pooled Phase 2b and 3 controlled clinical trial database not favoring dapagliflozin. In your initial NDA submission, there were nine cases of breast cancer in the dapagliflozin group versus one in comparator; all events occurred in female patients. The updated clinical trial data, submission of which extended the NDA review goal date, identified additional breast cancer cases in comparator groups reducing the risk estimate for this cancer. In your initial NDA submission, there were nine cases of bladder cancer reported in the dapagliflozin group compared to one case in the comparator group. All events occurred in male patients. The updated clinical trial data did not identify any additional cases of bladder cancer; however, the risk estimate remained concerning. The calculated incidence rate ratio for bladder cancer was 5.38. Although the

accompanying 95% confidence interval (CI) of 0.84-122.2 includes the possibility of a chance finding due to the lack of precision, the magnitude of the risk estimate (i.e., exceeding 5) is cause for concern.

Baseline characteristics of patients in the Phase 2b and 3 controlled clinical trials were well-balanced for risk factors that might contribute to the development of bladder cancer. Because dapagliflozin is associated with a higher rate of urogenital adverse events that could have resulted in more frequent monitoring, a thorough review of the case narratives was performed to determine if the imbalance in bladder cancer cases was due to a detection bias. No evidence of detection bias was identified.

2. Liver Safety

Imbalances in marked hepatic transaminase levels were not observed in your clinical development program. However, a case of biochemical Hy's Law (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x upper limit of normal (ULN) with serum total bilirubin > 2x ULN) was identified in the Phase 2b/3 pool. Although this case (D16900004-4402-6) was exhaustively reviewed by FDA hepatologists for another causative etiology, none could be identified. Therefore, it was deemed a probable drug-induced liver injury (DILI) case associated with dapagliflozin use.

3. Cardiovascular (CV) Safety

A meta-analysis of 14 Phase 2b and 3 controlled clinical trials was performed with the original submission of your NDA to evaluate CV safety of dapagliflozin. The primary endpoint was a composite of time to first event of CV death, myocardial infarction (MI), stroke, and hospitalization for unstable angina. All events were adjudicated in a blinded fashion by an independent endpoints committee. The pre-specified primary analysis compared all dapagliflozin treatment groups (excluding doses below 2.5 mg) to comparators (placebo and active controls). Seventy-eight cases were identified which yielded a hazard ratio point estimate of 0.67 (98% CI: 0.38-1.18) associated with dapagliflozin use. These findings were confirmed by FDA's sensitivity analysis on the primary composite endpoint and analyses of secondary endpoints also revealed similar point estimates. Overall, the results of this original meta-analysis were reassuring, if not suggestive of a CV benefit that might justify acceptance of the potential bladder cancer and liver safety risks.

To support the findings from the original meta-analysis, FDA requested an updated meta-analysis that would include data from trials ongoing at the time of the 4-month safety update and 5 additional trials, including Studies D1690C00018 and D1690C00019 (hereafter referred to as Studies 18 and 19). The updated meta-analysis of 19 controlled clinical trials included the same primary composite endpoint as proposed in the original meta-analysis and also included a secondary analysis of major cardiovascular events (MACE) with the composite endpoint of CV death, nonfatal MI, and stroke. An additional 67 CV primary composite endpoints were captured from the inclusion of the 5 new trials and the analyses of ongoing trials. The hazard ratio point estimate for both the primary composite endpoint and MACE endpoint were higher in the

updated meta-analysis than the original meta-analysis but still remained less than 1.0 and the upper bound of the 95% CI excluded both 1.8 and 1.3.

As noted above, the updated meta-analysis included results from Studies 18 and 19. These studies are 2-year studies in high CV risk patients with identical study design. The studies enrolled a similar patient population except that Study 18 *required* all patients to have a diagnosis of hypertension to be eligible. Adjudication of CV events was performed prospectively by a blinded endpoints committee and the methodology by which CV risk was to be assessed was aligned with FDA recommendations based on the FDA’s Guidance for Industry *Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, December 2008. The mean duration of treatment from these two studies at the time of the updated meta-analysis was approximately 6 months, but given the elevated baseline risks for CV disease, 60 events were captured. These two studies combined contributed approximately 40% of the total CV events in the updated meta-analysis. Because Studies 18 and 19 evaluated a similar and clinically relevant population for assessing CV risk in Type 2 Diabetes Mellitus (T2DM), were prospectively designed and executed to evaluate CV safety, and contributed approximately as many events as the original meta-analysis, separate CV analyses were performed in which data from only these two trials were considered. The results were discordant with the overall meta-analysis. The hazard ratio point estimates were no longer below 1.0 and the upper bound of the 95% CI was 1.77 for the primary composite and 2.31 for MACE.

Cardiovascular Meta-analysis of Studies 18 and 19

	Primary Composite Endpoint		MACE	
	Dapagliflozin	Comparator	Dapagliflozin	Comparator
Stratified HR (95% CI)	1.07 (0.64, 1.77)		1.26 (0.69, 2.31)	
Event/PY (% Incidence)	31/706 (4.39%)	29/706 (4.11%)	24/708 (3.39%)	19/709 (2.68%)
M-H Incidence Rate Difference (95% CI)	0.0028 (-0.018, 0.024)		0.0071 (-0.011, 0.025)	

While we cannot conclude that dapagliflozin is associated with excess CV risk based on an analysis of only these two trials, the findings from these two large, adequate, and well-designed trials in a relevant patient population cannot be ignored. More importantly, we cannot include any suggested CV benefit observed in the original meta-analysis in a risk-benefit consideration in regard to the cancer and liver safety signals.

Furthermore, while the glucose-lowering effect of dapagliflozin is the result of a novel mechanism of action that does not rely on insulin secretion or insulin sensitivity, the achieved HbA1c reductions are modest, and attenuated or absent in patients as renal function decreases. An anti-diabetic therapy that is ineffective in patients with moderate to severe renal impairment is a major limitation as many patients with T2DM have or will develop renal impairment.

Overall, the observed clinical benefits of dapagliflozin in your current clinical development program may be achieved with other available anti-diabetic therapies. In the absence of a unique benefit of dapagliflozin over these other therapies, an unmet need that may be filled by dapagliflozin could not be identified to offset the potential risks of bladder cancer and hepatic toxicity.

Path Forward

To address the above deficiencies, you will need to submit additional clinical trial data to increase the patient-years of exposure to dapagliflozin and comparators. At a minimum, the resubmission must include data from patients in Studies 18 and 19 who have completed at least 52 weeks of these trials. Analyses of the data should include the following:

- updated information on bladder cancer events and new risk estimates,
- updated review of hepatic safety, including cases that meet the definition of biochemical Hy's law with narratives of each case and incidence of transaminase elevations at 3x, 5x, 10x, and 20x ULN in both dapagliflozin and comparator groups, and
- updated CV meta-analysis including an analysis of MACE events.

We acknowledge your plans to initiate a CV outcomes trial in the fourth quarter of 2012. We strongly advise you to continue with those plans should data from that trial be necessary for consideration in a resubmission to this complete response.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
 7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

1. We have the following comment regarding product quality for you to address in your response to this letter. This request is not a basis for our inability to approve your application.

Your proposal to use disintegration as a surrogate for dissolution testing as part of the drug product regulatory specification is acceptable. However, we remind you that in vitro dissolution will be necessary to support certain post approval changes in accordance with existing FDA guidance documents and regulations. Additionally, ongoing registration stability studies should continue to monitor tablet dissolution and disintegration through the end of the study protocol. The following dissolution method is the application method for future comparative studies.

- USP Apparatus II (paddle), 60 rpm
- Acetate buffer, pH 4.5, 1000 mL at 37°C
- Limit: $Q = \text{[redacted]}^{(b) (4)}$ in 15 min; sampling profile at 5, 15, 30, and 60 minutes

2. In addition, we have following comment regarding future submissions from Bristol-Myers Squibb. This is not a request for an amendment to the financial information already submitted to this application.

Your financial disclosure package did not include specific details as to the size of the reported financial interests. As stated in our guidance *Financial Disclosure by Clinical Investigators*, March 2001, Q&A #16, “The applicant must disclose specific details of the financial interest including the size and nature of the financial interest in question” Therefore, the amount of each specific payment of other sorts (or other interests) should be provided rather than a statement that the amount exceeded the reporting minimum.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA’s Guidance for Industry *Formal Meetings Between the FDA and Sponsors or Applicants*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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, please call Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for 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/

CURTIS J ROSEBRAUGH
01/17/2012