

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee
July 19, 2011**

Topic: The committee discussed new drug application (NDA) 202293 dapagliflozin, manufactured by Bristol-Myers Squibb and AstraZeneca. Dapagliflozin is the first drug in the class of sodium-glucose co-transporter 2 (SGLT2) inhibitors, developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

These summary minutes for the July 19, 2011 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on 8-2-2011

I certify that I attended the July 19, 2011 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____**-Signed-**_____
Paul T. Tran, R.Ph
(Designated Federal Officer, EMDAC)

_____**-Signed-**_____
Abraham Thomas, M.D., M.P.H.
(Committee Acting Chair)

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting July 19, 2011

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on July 19, 2011. The verbatim transcript will be available in approximately six weeks, send to the Division of Metabolism and Endocrinology Products and posted on the FDA website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm>

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA, Center for Drug Evaluation and Research, met on July 19, 2011 at the Hilton Washington DC/Silver Spring, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Bristol-Myers Squibb (BMS)/AstraZeneca. The meeting was called to order by Abraham Thomas, M.D., M.P.H. (Acting Chair), and the conflict of interest statement was read into the record by Paul Tran, R.Ph. (Designated Federal Officer). There were approximately 350 people in attendance. There were three Open Public Hearing speakers.

Issue: The committee discussed new drug application (NDA) 202293 dapagliflozin, manufactured by Bristol-Myers Squibb and AstraZeneca. Dapagliflozin is the first drug in the class of sodium-glucose co-transporter 2 (SGLT2) inhibitors, developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Attendance:

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting):

Erica Brittain, Ph.D.; David Capuzzi, M.D., Ph.D.; Eric Felner, M.D.; Edward Gregg, Ph.D.; Ellen Seely, M.D.; Ida Spruill, Ph.D., R.N. (Consumer Representative).

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present (Voting):

Vera Bittner, M.D.; Lamont Weide, M.D., Ph.D.

Endocrinologic and Metabolic Drugs Advisory Committee Member Present

(Non-voting): Enrico Veltri, M.D. (Industry Representative)

Temporary Members (Voting):

Ed Hendricks, M.D.; Sanjay Kaul, M.D.; Kevin McBryde, M.D.; Cassandra McIntyre (Patient Representative); Steven Piantadosi, M.D., Ph.D.; Peter Savage, M.D.; Terry Smith, M.D.; Doris Strader, M.D.; Abraham Thomas, M.D., M.P.H. (Acting Chair).

FDA Participants (Non-voting):

Mark Avigan, M.D., C.M.; Somya V. Dunn, M.D.; Ilan Irony, M.D.; Mary H. Parks, M.D.; Curtis Rosebraugh, M.D., M.P.H.

Designated Federal Officer: Paul Tran, R.Ph

Open Public Hearing Speakers: Kelly L. Close (Editor, diaTribe); Diana Zuckerman, Ph.D. (President, National Research Center for Women & Families, Cancer Prevention and Treatment Fund); Sidney Wolfe, M.D. (Director of Public Citizen’s Health Research Group).

The agenda proceeded as follows:

<i>Call to Order and Introductions</i>	Abraham Thomas, M.D., M.P.H. <i>Acting Chair, EMDAC</i>
<i>Conflict of Interest Statement</i>	Paul T. Tran, R.Ph <i>Designated Federal Officer, EMDAC</i>
<i>Introduction/Background</i>	Ilan Irony, M.D. <i>Diabetes Clinical Team Leader</i> <i>Division of Metabolism and Endocrinology</i> <i>Products (DMEP)</i> <i>Office of Drug Evaluation (ODE) II</i> <i>Office of New Drugs (OND)</i> <i>Center for Drug Evaluation and Research (CDER)</i> <i>Food and Drug Administration (FDA)</i>
SPONSOR PRESENTATION	Bristol-Myers Squibb/AstraZeneca
<i>Introduction</i>	Amy Jennings, Ph.D. <i>Director</i> <i>Global Regulatory Sciences-US</i> <i>Bristol-Myers Squibb</i>
<i>Medical Need for New</i> <i>Anti-Diabetic Treatments</i>	John Buse, M.D., Ph.D. <i>Director of Diabetes Care</i> <i>University of North Carolina</i>
<i>Dapagliflozin: Overview of Mode</i> <i>of Action and Introduction to</i> <i>Development Program</i>	Elisabeth Svanberg, M.D., Ph.D. <i>Vice President, Development Lead- Dapagliflozin</i> <i>Bristol-Myers Squibb</i>
<i>Clinical Efficacy</i>	Shamik Parikh, M.D. <i>Executive Director</i> <i>Clinical Development CV/GI</i> <i>AstraZeneca</i>

Safety

Jim List, M.D., Ph.D.

*Executive Director
Global Clinical Research - CV/Metabolics
Bristol-Myers Squibb*

Overall Benefit -Risk

James Gavin, M.D., Ph.D.

*CEO & Chief Medical Officer of Healing Our Village,
Inc.*

Dapagliflozin Post-Approval

Brian Daniels, M.D.

*Senior Vice President
Global Development and Medical Affairs
Bristol-Myers Squibb*

*Clarifying Questions from the
Committee*

BREAK

FDA PRESENTATION

Overview of Efficacy

Jonathan Norton, Ph.D.

*Statistician, Division of Biometrics II (DBII)
Office of Biostatistics (OB)
Office of Translational Sciences (OTS), CDER, FDA*

Safety Issues

Somya V. Dunn, M.D.

*Clinical Reviewer
DMEP, ODE II, OND, CDER, FDA*

*Clarifying Questions from the
Committee*

LUNCH

Open Public Hearing Session

*Questions to the
Committee/Committee Discussion*

BREAK

*Questions to the
Committee/Committee Discussion*

ADJOURNMENT

Questions to the Advisory Committee:

Efficacy

1. Dapagliflozin's efficacy is dependent on the amount of glucose filtered through the glomeruli. As the glomerular filtration rate (GFR) declines in renal impairment, the efficacy of the SGLT-2 inhibitor is also diminished. Please discuss the implications of this reduced efficacy in Type 2 Diabetes Mellitus (T2DM) where renal impairment can impact a sizeable proportion of patients with this disease. Please include in your discussion whether additional studies (e.g., in special populations) should be conducted to better characterize the efficacy of dapagliflozin in T2DM or whether monitoring for renal function should be performed prior to and/or during treatment with dapagliflozin.

Committee Discussion: *The committee expressed concerns regarding a cut-off point of 45 ml/min for the GFR as they agreed that this was an arbitrary number. Therefore, the committee suggested additional studies be performed to assess creatinine clearance and/or GFR cut-offs using measurements other than the estimated GFR formula. Based on the data provided by the sponsor, it appeared that there was no benefit in patients whose GFR is below 60 ml/min, thus a prospective trial would need to be performed in order to demonstrate efficacy in these patients. Another concern that was raised by the committee was in regards to the classification system used for kidney disease. The system, which does not exist in the U.S., separated kidney disease into two categories (3A and 3B). The committee felt that this separation might be confusing for clinicians in the U.S. In addition to their concerns, the committee suggested that the sponsor reanalyze their data for estimated GFR since different formulas were used in different countries. The committee also recommended that monitoring for renal function be done consistently during treatment with dapagliflozin in order to ensure that efficacy is still present. Additionally, scheduling of renal monitoring should be consistent with other types of monitoring in diabetes patients in order to reduce the burden on patients.*

Please see the transcript for details of the committee's discussion.

Hepatic Safety

2. Five patients treated with dapagliflozin developed ALT or AST > 3x ULN with accompanying total bilirubin > 2x ULN (biochemical Hy's law). An adequate explanation for the biochemical abnormalities could be identified in all but one case. This one case was classified as a 'probable diagnosis of mild to moderately severe dapagliflozin-induced liver injury'. Imbalances in severe hepatic transaminase elevations (> 5x and 10xULN) between dapagliflozin and comparators were not observed and no signal for hepatotoxicity was identified in the nonclinical program.

Please comment on the clinical relevance of the one case and whether sufficient evaluation has been conducted premarketing to determine if dapagliflozin is associated with a risk of hepatotoxicity.

Committee Discussion: *The committee was concerned with the one case of "probable dapagliflozin-induced liver injury", and commented that it was unlikely due to an autoimmune*

disease. It was mentioned that diabetes patients who are obese may have an underlying disease pattern, such as a high rate of nonalcoholic steatohepatitis (NASH), before initiation of the medication. Also, concomitant medications, such as statins, could have clouded the true cause of liver injury/function. The committee also voiced concerns that other racial and ethnic groups were poorly represented in the trials, thus the potential differences in drug metabolism for different racial and ethnic groups should be further explored. In addition, there should be more clearly defined liver testing, frequency of testing, and criteria set forth for clinicians to identify risk factors. Also a protocol for testing and follow-up for patients who are identified to have changes in liver function while on the drug should be in place rather than leaving this up to the individual physician at the research site.

Please see the transcript for details of the committee's discussion.

Breast and Bladder Cancer

3. Numeric imbalances in breast and bladder cancer were observed in the clinical development program. For both of these types of cancer, please discuss whether these imbalances signify a risk of carcinogenic potential associated with dapagliflozin. In addition, please comment on whether the numeric imbalances were impacted by the following:

- a. Any imbalance of baseline risk factors
- b. Any detection bias

Committee Discussion: In terms of risk factor, the committee expressed uncertainty about the data that was presented as some degree of detection bias was possible in subjects who lost weight since it would have been easier to detect breast cancer or a mass via a mammogram or other methods. Dehydration, a side effect of the drug, was also mentioned as a potential detection bias for breast cancer. Similarly, there could have been detection bias for bladder cancer due to the frequent testing for urinary tract infections which could have led to the discovery of microscopic hematuria. However, the committee felt that detection bias could not explain overall risks in terms of the number of cases. Some of the members commented that there was a gender difference in the number of cases of bladder cancer in patients on the drug. Some of the imbalances in the number of cases of bladder cancer seen in the studies could have been explained by known differences in the risk for bladder cancer between genders. It was emphasized that screening should be stringent to assess the risk of breast or bladder cancer in patients prior to enrollment into future trials.

Please see the transcript for details of the committee's discussion.

Other Safety Findings

4. Please discuss the clinical significance of the following in the T2DM population:

- a. increased genital-urinary infections associated with dapagliflozin therapy
- b. bone safety concerns
- c. any other safety issues identified in the premarketing application

Committee Discussion: The committee noted that there was a clear imbalance between the placebo and treatment groups for genital-urinary infections. In addition, there appeared to be an

increased risk for secondary infection in the treatment group. The committee felt that longer term data was necessary to assess whether this was a true risk. Another concern that was raised was that patients treated with dapagliflozin were at an increased risk for experiencing multiple episodes of urinary infections which might lead to over-use of antibiotics, and potential antibiotic resistance in the long run. The committee did not express major concerns with bone safety, but felt that additional monitoring of bone turnover would be helpful. Other safety issues identified included dehydration, reduced creatinine clearance, and the loss of calories in the urine of subjects with nutritional imbalance. Further studies could examine nutritional balance by checking the 24- hour nitrogen or protein clearance. The committee expressed that there are many unknowns with these safety issues; however, there was less concern with the breast and bladder cancers signals.

Please see the transcript for details of the committee's discussion.

Voting Question

5. Do the efficacy and safety data provide substantial evidence to support approval of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM?

(VOTING) **Yes: 6 No: 9**

- a. If yes, do you recommend any further data be obtained post-marketing?
- b. If no, what further data should be obtained?

Committee Discussion: *The majority of the committee members concurred that the efficacy and safety data did not provide substantial evidence to support approval of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Some members who voted "No" indicated that they struggled with their decision and as they could have voted "Yes" since dapagliflozin proved efficacious in reducing HbA1c, but the potential signals for breast and bladder cancers in addition to the potential for liver toxicity were concerns. Thus, these panel members felt that additional safety data is necessary prior to approval. The committee further recommended that data be obtained in minority patients, the elderly, patients with hepatic insufficiency and patients with mild to moderate renal impairment. Also, longer term trials should be conducted to collect further data on patients with genital and urinary tract infections. One panel member who voted "Yes" recommended that post-marketing studies be conducted to evaluate why there is an unmasking of cancers and registries or surveillance to monitor for cancers when patients are receiving the drug.*

Please see the transcript for details of the committee's discussion.

The meeting was adjourned at approximately 4:37 p.m.