Testimony of Sidney Wolfe M.D.
Health Research Group of Public Citizen

Endocrine and Metabolic Drugs
Advisory Committee

Dapagliflozin: July 19, 2011

(I have no financial conflict of interest)

Factual Agreements About Dapagliflozin

- First of a new chemical class of agents for type 2 diabetes mellitus (T2DM)
- First T2DM drug to act at the renal sodium-glucose transport protein, subtype 2 (SGLT-2)
- Approval request based solely on surrogate efficacy:
  HbA1c lowering, as with previous T2DM drugs
- No evidence of any improved clinical outcomes (contrary to an older drug such as metformin)
- The overall question, according to the FDA, is:

  "The [surrogate] efficacy of dapagliflozin needs to be balanced against safety signals identified in the clinical trials."

Principle Safety Problems found in Clinical Trials

- Bladder cancer: 9 cases/dapa pts; 1 case/controls
- Breast cancer: 9 cases in dapa pts; 0 cases/controls
- One probable Hy's Law hepatotoxicity case, classified as a 'probable diagnosis of mild to moderately severe dapagliflozin-induced liver injury'.
- Increased genital and urinary tract infections
- Chronic osmotic diuresis with cases of pre-renal azotemia, hypovolemia and risks of dehydration, heat intolerance, especially in elderly using diuretics

Bladder Cancer Risk

- “the baseline characteristics of risk factors for bladder cancer in the dapagliflozin-treated patients and the control group were similar (Table 11), reducing the likelihood that any such imbalance of risk might have contributed to the numerically higher number of cases observed with dapagliflozin. (FDA briefing document, page 24)
- With nine cases of bladder cancer [dapa pts] occurring during this time, this rate amounts to 299.3 (95% CI, 136.6 – 568.1) new cases per 100,000 subject-years. This compares to one case during 1696.6 subject-years in controls, or 58.9 (95% CI, 0.8 – 327.9) new cases per 100,000 subject-years. The incidence rate ratio between active treatment and control was 5.08 (95% CI, 0.70 – 222.6), two-sided p=0.15 (Fisher's exact). (FDA correction to briefing document)

Bladder Cancer Risk (cont'd)

- Based on SEER data, only three (3.03) cases of bladder cancer would be expected in the male dapagliflozin exposed population at a rate of 100.6 new cases per 100,000 subject years. The standardized incidence ratio of observed versus expected cases in males exposed to dapagliflozin was 2.98 (95% CI, 1.36 – 5.65), p=0.008. Almost 2 cases (1.87) would be expected among controls, where only case was observed. (corrected FDA review documents)

- "the clinical trials were not powered to statistically distinguish between 9 cases of bladder cancer in the active treatment arms compared to 1 case in the control arms. However, event rates for males observed in the active treatment arms significantly exceeded the rates expected in an age-matched reference diabetic population. (Dr. Hampp, p 75 FDA briefing document)

Breast Cancer Risk

- “Breast cancer risk factors at baseline were similar between the dapagliflozin treated patients and the control patients.” (Table 13) (FDA briefing document, p. 26)
- With nine cases of breast cancer observed in the female dapagliflozin-treated patients versus none in the comparator arms of the dapagliflozin clinical trials, it is technically not feasible to estimate the incidence rate ratio….[T]hat the age-specific incidence rates of breast cancer were higher than those reported in the literature could be a safety signal that dapagliflozin may be associated with an increased risk of breast cancer. The SIR calculated by the sponsor using SEER data as an external reference group may be underestimated and is not reassuring due to study limitations.” (FDA briefing document, p. 65)

Hepatotoxicity

"pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury." (2007 Draft FDA guidance on liver toxicity)

"Finding one Hy's Law case in the clinical trial database is worrisome…Clinical trials of tasosartan, an angiotensin II blocking agent, showed a single Hy's Law case. This led to a request for a much larger premarketing database and the drug was abandoned." (FDA briefing document, p. 79)

Recent examples of some drugs causing idiosyncratic hepatotoxicity (e.g., bromfenac, troglitazone, ximelagatran) further illustrate the predictive value of Hy's Law, where findings during clinical trials were noted and severe DILI occurred after marketing….

Hepatotoxicity (cont'd)

FDA staff expressed concerns about the incompleteness of ascertaining whether there were other Hy's Law cases, stating:

"In this review, an analysis of protocols for the monitoring serum liver biochemistry values and study protocol adherence has not been performed. Moreover, any potential impact of study subject drop-outs and loss to follow-up has not been analyzed in this review. There are a number of other cases that lack sufficient data to link them to treatment with dapagliflozin……..

because of the importance of recognizing sentinel cases of DILI in registrational trials as outlined in the 2009 pre-marketing guidance[8] it is prudent to gather more information on all relevant cases as part of an in-depth review of the dapagliflozin NDA. in order to assess whether this agent may be hepatotoxic." (FDA briefing document, p.88)

Genital and Urinary Infections

- Significant increase in total of vulvovaginal mycotic infections and vaginal infections with all dapa patients (78/3291= 2.4%) compared with placebo patients (6/1393=0.5%)(FDA briefing document p. 33, table 16)
- Urinary tract infections significantly increased in all dapa patients (131/3291=4%) compared with placebo patients (38/1393=2.7%) (FDA briefing document p. 37, table 21)
- The findings of increased mycotic infections in dapa patients whose HbA1c was lower than the placebo patients is particularly striking since in diabetic patients, there is a significant link between hyperglycemia and vulvovaginal candidiasis. (J. Infect. 2004;21:162-6). This points to the role of constant, significant glycosuria in these infections.

Events related to Chronic Intermittent Osmotic Diuresis and Volume Depletion

There was an increase in patients with volume depletion events in people randomized to dapa--such as hypotension, mainly after three weeks of therapy—compared with patients getting a placebo.

(placebo, 5 events/1303 patients=0.4%) vs all dapa patients, 24 events/3291patients=0.7%)

Although this did not reach statistical significance (p=0.10), there is still a high probability of its relationship to dapa, especially because of the clear biologic plausibility.

(FDA briefing document, p.48)

Decreases in estimated GFR and increases in blood urea nitrogen relative to serum creatinine suggest development of prerenal azotemia (FDA briefing document pp. 40-41)

Summary of Dapagliflozin Benefit / Risk Balance

For a drug that offers a new mechanism of HgA1c-lowering devoid of any evidence of clinical benefit, the long list of FDA's serious concerns, quoted below, argues strongly, in my view, against approving dapagliflozin:

"the imbalance in cases of bladder cancer and breast cancer not favoring dapagliflozin, a potentially serious case of drug-induced liver injury (meeting the biochemical threshold for "Hy's Law"), the unknown long term effect of increased urinary infections and genital infections on renal function and reproduction, as well as the short term risks to renal function related to hypovolemia and dehydration in the elderly and in those patients on diuretic and antihypertensive therapy."