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Endocrinologic and Metabolic Drugs Advisory Committee

Dapagliflozin: December 12, 2013

(We have no financial conflict of interest)

Public Citizen Testimony on Dapagliflozin from 7/19/11 AC meeting

- 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." (vote 9 to 6 against approval)

Situation now with 2013 canagliflozin approval

- **Would be the second** of a new chemical class of agents **approved** for type 2 diabetes mellitus (T2DM)
- **Would be the second approved** T2DM drug to act at the renal sodium-glucose transport protein, subtype 2 (SGLT-2)
- Approval 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 question, according to the FDA, is:

  "The [surrogate] efficacy of dapagliflozin needs to be balanced against safety signals identified in the clinical trials" **and, now, also compared to safety signals with canagliflozin**

Reasons why dapa decision should depend on comparative (with cana) safety determinations

- Surrogate efficacy (HbA1c) effect is not significantly different between dapa and cana
- Cardiovascular risks, genital infections, polyuria, hypovolemia, hypotension, increased LDL, are also similar for the two drugs but…
- Several other major risks of dapa are not present with cana. These will be discussed.
- Had the **original dapa review** followed, rather than preceded, the cana approval, the vote against its approval would likely have been even more negative than it was (6 for, 9 against), because of the unfavorable safety comparison with cana.

Main Safety Problems in Dapa Clinical Trials
(as of 7/11 AC meeting, prior to comparative cana data)

- Bladder cancer: 9 cases in dapa pts; 1 in controls
- Breast cancer: 9 cases in dapa pts; 1 in 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

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Bladder Cancer Risk: dapa

- “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 7/19/11 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 7/19/11 briefing document)

Dapa Cana RCT Comparisons: Bladder Cancer

Study Groups	Drug patients	Control patients	Cancers Drug	Cancers control	P value: Chi square (Yates) ***
Dapa vs control *	5936	3403	9	1	**P=0.15**
Cana vs control **	6648	3640	5	4	**P=0.83**

*** FDA dapa brief document, page 28**

**** FDA cana brief document page 30 (clinical)**

***** Recommended analysis: FDA brief had risk ratios only**

Public Health Implications of p=0.15

Although not statistically significant by the standard ($p < 0.05$) used for evaluation of efficacy, there is nevertheless useful information in such a finding, especially considering the lack of evidence of any dapa benefit compared to canagliflozin.

p=0.15 means that there is only a 15% probability that this increased bladder cancer with dapagiflozin could occur by chance. In contrast, for canagliflozin,

with p= 0.83, there is an 83% probability that this difference can be explained by chance, i.e. that the drug is not associated with bladder cancer.

Efforts to wish away bladder cancer evidence

"Flexible", conflicting industry attitudes on animal carcinogenicity vs human cancer

If a chemical/drug *only causes cancer in animals*, despite underpowered ability for human detection, it is "not really a human carcinogen" but...

If human cancer is found in an RCT with indistinguishable baseline characteristics in both groups, *but animal evidence is lacking*—again, it is "not really a human carcinogen"

BMS/AZ preclinical/animal attempts to “refute” human evidence

Dapa did not:

- cause in vitro stimulation of human bladder transitional cell carcinomas (TCC) cell lines
- increase the size of human TCC tumors implanted in mice.
- cause transcriptional changes characteristic of tumor promoters in a ZDF rat model.

Increased glucose concentrations did not:

increase the rate of growth in TCC cell lines

FDA response to these studies

- each of these experimental approaches had deficiencies in terms of limitations or relevancy. Results of these studies confirm …what the FDA already concluded: that dapagliflozin by itself does not act as a carcinogen. *Any putative human bladder risk from dapagliflozin would likely be related to tumor promotion secondary to changes in the microenvironment of the bladder in vivo.*

FDA Briefing document, page 22

Case study of human cancer also missing animal evidence

- Inorganic arsenic: According to the partially NIH-funded International Agency for Research on Cancer (IARC), “over the years, it has been difficult to provide [animal] evidence for the carcinogenesis of inorganic arsenic compounds”
- More recently, with animal “exposure to inorganic arsenic during early life”, the links have been found.
- **Animal evidence was found, experimentally, long after human evidence of arsenic-induced bladder cancer.**

Arsenic, Metals, Fibres and Dusts: IARC Monograph, 2012

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Breast Cancer Risk

- “Breast cancer risk factors at baseline were similar between the dapagliflozin treated patients and the control patients.” (Table 13) (FDA 7/19/11briefing 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)

FDA Consultation on Breast Cancer

- “the decline in the incidence risk ratio over time, the lack of screening mammography prior to study entry coupled with the occurrence of the breast cancers within the first year of dapagliflozin therapy, the median time from diagnosis of diabetes of seven years, the history of prior exposure to other oral hypoglycemic agents, and the hormone receptor positivity of the breast cancers suggests that the increased incidence of breast cancer is a spurious finding. “

FDA current briefing document, page 27

To call this a spurious finding in light of the extremely close baseline characteristics and the randomized nature of the study is itself somewhat questionable.

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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….

Absence of Hy's Law case with canagliflozin

"there was an imbalance in marked shifts in transaminases not favoring canagliflozin, but review of cases that met the Biochemical criteria of Hy's law (AST or ALT ≥3x ULN and total bilirubin ≥2x ULN) …did not identify any true Hy's law cases. Thus…absence of a Hy's law case is somewhat reassuring."

FDA Cana Briefing Document, pages 88-89

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Dapa Genital and Urinary Infections
(from 7/19/11 FDA briefing material)

- 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 7/19/11 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)

- Both cana and dapa have significantly increased genital mycotic infections (from cana briefing documents)

Dapa Cana RCT Comparisons: Urinary Tract Infections

Study Groups	Drug patients	Control patients	Drug UTIs	Control UTIs	P value: ***Chi square (Yates)
Dapa vs* placebo	2026	1956	174 **(8.2%)**	121 **(6.2%)**	**P=0.005**
Cana vs** placebo	5733	2706	320 **(5.6%)**	124 **(4.6%)**	**P=0.06**

* Table 23: FDA briefing document today:
** Table 44: FDA cana briefing document 1/10/13

*** Recommended analysis: FDA brief had risk ratios only

Events related to Chronic Intermittent Osmotic Diuresis and Volume Depletion

There was an increase in 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%
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 7/19/11, 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)

Dapagliflozin and Canagliflozin Common Features

- Efficacy of both is based solely on surrogate efficacy: HbA1c lowering, as with previous T2DM drugs, without evidence of any improved clinical outcomes (contrary to an older drug such as metformin)

- Cardiovascular risks, genital infections, increased LDL are also similar for the two drugs as are intermittent osmotic diuresis with polyuria, hypovolemia, hypotension and risks of dehydration, heat intolerance, especially in elderly.

Dapagliflozin and Canagliflozin Differences

- Bladder cancer: RCT shows p value of risk difference on dapagliflozin =0.15, for canagliflozin, 0.83
- Hy's Law case for dapa, none for cana: "probable diagnosis of mild to moderately severe dapagliflozin-induced liver injury" "Finding one Hy's Law case in the clinical trial database is worrisome."
- Asymmetry with urinary tract infections: dapa increase p=.005; cana p=0.06

- Both drugs have indistinguishable efficacy and common safety problems that are cause for concern

- But dapagliflozin has additional hazards not present with canagliflozin.

- We agree with FDA's assessment that: "As a result of these updated analyses the Agency could not conclude with any level of confidence that the purported CV-benefit associated with dapagliflozin use outweighed the observed imbalance in specific malignancies or potential liver toxicity risks."

- We urge this committee to vote against approval.