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Endocrine and Metabolic Drugs
Advisory Committee

Canagliflozin: January 10, 2013

(I have no financial conflict of interest)

Factual Agreements About Canagliflozin

- Second of a new chemical class of agents for T2DM being considered for approval (the first not approved as of now)
- First T2DM drug class to act at SGLT-2 renal receptor
- Approval request based solely on surrogate efficacy: HbA1c lowering, as with all recently approved T2DM drugs
- No evidence of any improved clinical outcomes (contrary to an older diabetes drug such as metformin)

This surrogate efficacy of canagliflozin needs to be balanced against clinical safety signals identified in the clinical trials.

Principle Safety Problems found in Clinical Trials

- Chronic osmotic diuresis with decreased eGFR, early hypovolemia and risks of dehydration, especially likely in elderly using diuretics
- Strong signals of increased cardiovascular risk including increase in events in the first 30 days, significant elevations in LDL cholesterol, increases in hematocrit probably because of volume depletion
- Increased genital and urinary tract infections

Events related to Chronic Intermittent Osmotic Diuresis and Volume Depletion

dapagliflozin:

There was an increase at 24 weeks in patients with volume depletion events such as hypotension in those randomized to dapa compared with patients getting a placebo.

placebo: 5 events/1393 patients=0.4%

all dapa: 24 events/3291patients=0.7%

This did not reach statistical significance (p=0.22), but there is still a high probability of its relationship to dapa because of the unequivocal biologic plausibility.

(FDA dapa briefing document, p.39)

Events related to Chronic Intermittent Osmotic Diuresis and Volume Depletion

canagliflozin:

There was an increase after 30 days of therapy in volume depletion events in people randomized to cana versus patients getting a placebo

placebo: 1 event / 382 patients=0.3%

all cana: 16 event / 702 patients =2.3%

Unlike the data on dapa, this did reach statistical significance (p=0.009), not surprising because of the apparently greater volume depletion with cana, as also evidenced by hemo-concentration.

(FDA briefing document, study DS2, moderate renal impairment, page p.35)

Early cardiovascular (CV) events in dedicated cardiovascular outcomes trial *

During the first 30 days after randomization:

13 CV events occurred on cana (0.45%)

1 CV event occurred on placebo (0.07%).

"The estimated hazard ratio during the first 30 days was 6.50, with 95% CI 0.85, 49.66; not significant due to small number of events." FDA concluded that: "these early CV events may be related to canagliflozin-induced volume/diuretic changes which occur shortly after initiating canagliflozin."

*DIA3008 (CANVAS): from p. 75 of FDA brief document: In subjects with a high baseline risk for cardiovascular disease.

Evidence of Hemo-concentration

	Mean Increase in hematocrit (%)	
	Low dose	High dose
dapaglifozin	1.57	2.15
canagliflozin	2.4 (1.53 x mean)	2.6 (1.21 x mean)

FDA Diabetes Guidance

"Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two sided 95 percent confidence interval for the estimated risk ratio is less than 1.8."

Table 3. Number of Events (Rate per 1000 Patient-Years) in All Trials in the Pre-Specified Meta-Analysis

	Canagliflozin N= 6396 PY = 6876	Comparators N = 3327 PY = 3470	Hazard Ratio (95% CI)
MACE-plus	**130 (18.9)**	**71 (20.5)**	**0.91 (0.68, 1.22)**
CV Death	21 (3.1)	16 (4.6)	0.65 (0.34, 1.24)
MI	45 (6.5)	27 (7.8)	0.83 (0.51, 1.34)
Stroke	47 (6.8)	16 (4.6)	1.46 (0.83, 2.58)
Hospitalized unstable angina	26 (3.8)	18 (5.2)	0.71 (0.39, 1.30)

Source: Created by reviewer

Despite Guidance, the largest Mace component, stroke, has upper bound of 2.58

Effect of Canagliflozin on Renal Function

Because of volume depletion, there is a concern for potential adverse renal effects. Canagliflozin has been associated with dose-dependent decrease in eGFR, different with different baseline renal function. In DIA3008, which enrolled subjects with moderate renal function the early drop in eGFR appear to persist over time. In addition, evaluation of marked changes in eGFR showed that the incidence of marked decline in eGFR was similarly greater with both doses of canagliflozin compared to placebo in subjects with moderate renal function.

FDA Briefing, Page 89

FDA Concern about effectiveness of lowering dose in people with moderate renal function

Because of increased volume with canagliflozin with low baseline eGFR, the company proposes 100 mg dose of canagliflozin as the starting dose for subjects with moderate renal function. But the glycemic efficacy in subjects with moderate renal function is modest, with further attenuation of glycemic efficacy in those at the lower end of moderate renal function (e.g., <45 mL/min/1.73m2). Thus, subjects with moderate renal function will be at an increased risk for adverse renal events with [only] moderate efficacy.

Answers from FDA Renal Consultants

"the observed changes in renal function are secondary to volume depletion. Although one would expect reversibility following drug discontinuation and correction of volume depletion, the applicant has not provided data that speak to the long term renal consequences of extended exposure to the drug in the proposed population"

Answers from FDA Renal Consultants (cont)

it seems prudent to assume that the volume depletion and corresponding reduction in eGFR caused by canagliflozin places patients at increased risk for clinically significant episodes of acute kidney injury (AKI) ….larger treatment effects on eGFR will translate into greater risk…. The amount of safety data in subjects with diabetes and moderate renal impairment is limited and what data exist suggest a high absolute risk of potentially clinically meaningful episodes of AKI at both doses and, in particular, at the high dose…related to the presence of underlying renal disease, age, concomitant therapies commonly used in this population (such as diuretics), or a combination of these and possibly other factors.

Summary of Canagliflozin 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 against approving canagliflozin:

- short term and long-term risks to renal function related to hypovolemia and dehydration in the elderly and in those patients on diuretic and antihypertensive therapy
- the extremely troublesome early (30 day) increase in CV events in an enriched population coincident with early (30 day) significant volume depletion
- the unknown long term effect of increased urinary infections and genital infections on renal function and reproduction