CLOSER LOOK

MEMORANDUM

FDA adds warning for increased risk of leg and foot amputations to labels for J&J's canagliflozin franchise, including Invokana, Invokamet, and Invokamet XR - May 16, 2017

Executive Highlights

- The FDA is requiring the addition of a new boxed warning for increased risk of leg and foot amputations to the labels for J&J's canagliflozin products (including Invokana, Invokamet, and Invokamet XR).
- Leg and foot amputations (most commonly of the toes) occurred about twice as often in patients treated with canagliflozin compared to those treated with placebo in CANVAS and CANVAS-R. Full results will be detailed at ADA 2017.

The FDA announced today that it is requiring the addition of a boxed warning for increased risk of leg and foot amputations to the labels for J&J's Invokana (canagliflozin), Invokamet (canagliflozin/metformin), and Invokamet XR. This conclusion is based on the full results from the CANVAS cardiovascular outcomes trial and CANVAS-R renal outcomes trial, which are to be presented in just a few short weeks at ADA 2017. Topline results have not been released, but according to the FDA's updated Drug Safety Communication leg and foot amputations (most commonly of the toes) occurred about twice as often in patients treated with canagliflozin compared to those treated with placebo: CANVAS showed amputation rates of 5.9/1,000 patient-years with canagliflozin (versus 2.8/1,000 patient-years with placebo) and CANVAS-R showed amputation rates of 7.5/1,000 patient-years with canagliflozin (versus 4.2/1,000 patient-years with placebo). The FDA advised patients taking canagliflozin to contact their HCPs if they notice new pain, tenderness, sores, ulcers, or infections in their legs or feet, and urged health care professionals to consider factors that may predispose patients for amputations (a history of prior amputation, peripheral vascular disease, neuropathy, diabetic foot ulcers) before prescribing canagliflozin, and to carefully monitor canagliflozin patients for these signs and symptoms.

The FDA began investigating the potential risk for increased amputation risk with canagliflozin in May 2016 based on an interim analysis from CANVAS and CANVAS-R, and the EMA initiated its own safety review a month prior which was later expanded to include the other two agents in the SGLT-2 inhibitor class in July 2016. Notably, the EMA took a "better safe than sorry" approach and recommended label warnings for all three SGLT-2 inhibitors, despite acknowledging that no increased risk has been observed in studies for AZ's Farxiga (dapagliflozin) and Lilly/BI's Jardiance (empagliflozin) thus far. It's unclear what the mechanism of risk is and we are anxiously the presentation of full results from the CANVAS program at ADA to learn more about the increased incidence of amputations with canagliflozin. In a break from what seems to have become at least somewhat more standard practice, J&J has not released topline results from CANVAS and questions abound about cardiovascular and renal impact of canagliflozin. Also on the safety front, we'll be keeping a close eye out for DKA and bone fracture risk data, both of which are included as warnings on Invokana's label as well.

- **We are not sure whether this news will spur the FDA to request information on amputations from other SGLT-2 inhibitor manufacturers as well.** The amputation rates in the long-term EMPA-REG OUTCOME trial of Jardiance were not reported in the published paper, suggesting that there were no concerning signals, and we have not heard anything specific about an increased risk associated with Farxiga. That said, as noted above, the EMA chose to extend the warning to all three members of the class in an abundance of caution in our view. The lack of any

previous mechanistic or clinical evidence suggesting a link between SGLT-2 inhibitors and amputation risk leads us to suspect that this effect may be something specific to the canagliflozin molecule, and we are curious to see how this will affect the product's performance within the greater SGLT-2 inhibitor market, where it currently leads by value due largely to its first-to-market status in the US. We imagine that empagliflozin may increasingly become the SGLT-2 inhibitor of choice for many patients and providers, given its CV mortality indication and its lack of safety warnings for lower limb amputation, bone fracture risk, or acute renal failure.

-- by Abigail Dove, Helen Gao, and Kelly Close