CLOSER LOOK

MEMORANDUM

FDA approves new indication for Jardiance (empagliflozin) for the reduction of cardiovascular death - December 2, 2016

Executive Highlights

- The FDA approved a new indication for Lilly/BI's Jardiance (empagliflozin) for the reduction of cardiovascular death in people with type 2 diabetes on the basis of the EMPA-REG OUTCOME results.
- Jardiance is the first-ever diabetes medication to be approved for this indication.

In extremely exciting news earlier today, the FDA approved a new indication for Lilly/BI's Jardiance (empagliflozin) for the reduction of cardiovascular death in people with type 2 diabetes. This new label update - the first of its kind for a diabetes drug - is based on the results of the EMPA-REG OUTCOME study, which elicited thunderous applause at EASD 2015 by demonstrating an impressive 38% risk reduction for cardiovascular death with empagliflozin compared to placebo (HR=0.62, 95% CI = 0.49-0.77; p<0.001). We have been awaiting the FDA's decision on this label update since the Advisory Committee hearing in June. Although the panel ultimately voted in favor of an additional cardiovascular mortality indication for Jardiance, the margin was razor-thin (12-11!), largely due to controversy over whether a single trial designed to demonstrate cardiovascular safety for a 3-point composite MACE (cardiovascular death, non-fatal MI, and non-fatal stroke) primary endpoint could support a label claim of benefit for the secondary endpoint of standalone cardiovascular death reduction. Although death is a secondary endpoint, well-respected biostatistician Dr. Stuart Pocock argued at the Advisory Committee meeting that the cardiovascular death finding was both incredibly statistically persuasive ("overwhelming evidence of benefit" and "proof beyond a reasonable doubt") and clinically meaningful. As expressed by our very own Ms. Emily Regier and Ms. Helen Gao during the AdComm's open public hearing (see their remarks here and here), we believe the addition of this cardiovascular indication to Jardiance's label adds enormous value in terms of increasing awareness of the groundbreaking and unprecedented EMPA-REG OUTCOME findings among diabetes patients and their providers. Furthermore, we expect the label update will provide an important impetus for discussions of the cardiovascular risks associated with diabetes among patients and providers and serve an important source of leverage in formulary access negotiations.

A similar indication for Lilly/BI's SGLT-2 inhibitor/metformin fixed-dose combination Synjardy (empagliflozin/metformin) remains under FDA review. The EMPA-REG OUTCOME results were not submitted to regulatory authorities for DPP-4 inhibitor/SGLT-2 inhibitor fixed-dose combination Glyxambi (linagliptin/empagliflozin) and it's unclear to what extent the cardiovascular benefit will be extrapolated to this product in the eyes of the public (though, of course, Lilly/BI are unable to promote the benefit without a label update).

- **We spoke with BI's VP of Clinical Development and Medical Affairs Dr. Thomas Seck, who emphasized that the FDA's announcement marks today as a "very important day for patients with type 2 diabetes and cardiovascular disease."** Approximately two-thirds of diabetes deaths are cardiovascular in nature, so Jardiance, as the first-ever diabetes medication to receive an indication for reducing the risk of cardiovascular death, addresses a staggering previously unmet need. Citing Lilly/BI's recent national survey on diabetes and cardiovascular disease, Dr. Seck noted that an overwhelming 66% of individuals living with type 2 diabetes are unaware of their heightened risk for CV morality, and that more than 50% do not realize their increased risk for CV events in general, including heart attacks, strokes, and death. He expressed optimism that Jardiance's label update, in addition to offering a treatment for this, will increase patient awareness

of the cardiovascular complications of diabetes. According to Dr. Seck, a key effort moving forward will be to educate both patients and various types of physicians - including endocrinologists, primary care physicians, and now even cardiologists - about Jardiance's cardiovascular effects. We've seen immense enthusiasm among cardiologists for the cardioprotective benefits of empagliflozin, with many viewing the drug as a cardiovascular medication rather than a diabetes medication and encouraging their colleagues to begin prescribing it themselves.

- **Expert cardiologist Dr. Christopher Cannon (Harvard Medical School, Boston, MA) shared in a separate call with us that this expanded Jardiance indication officially invites cardiologists into diabetes treatment.** He described a "paradigm shift" that has sprung into motion - cardiologists can now play a more active role in diabetes care (as they should, given the massive overlap between diabetes and CV disease) and can prescribe a type 2 diabetes therapy to patients in their office. Moreover, he highlighted that that this FDA decision signals a sharpened focus on outcomes: "Now we're choosing therapies that are proven to improve outcomes, not just proven to lower glucose to a certain level." We were thrilled to hear such enthusiasm from Dr. Cannon, and we absolutely love the idea of cardiologists becoming even more integrated into diabetes management. We also note that all cardiologists at the AdComm voted "yes" in favor of the Jardiance label change.
- **We are eager to see how this new indication will affect Jardiance sales and payer reimbursement.** According to Lilly's 3Q16 earnings update, total worldwide Jardiance revenue (including BI's share) was ~$144 million in 3Q16 based on our estimates, approximately tripling in YOY growth. This far outpaces the overall SGLT-2 inhibitor market, which grew 33% YOY to just under $700 million in 3Q16. AZ's Farxiga (dapagliflozin) currently leads the class in TRx, with J&J's Invokana (canagliflozin) at 27% and Jardiance at 22%. Jardiance has been showing very strong upward trajectory in TRx in recent years, and we imagine this trend will accelerate now that Jardiance has differentiated itself with the cardioprotection indication. Lilly management has repeatedly suggested that a label update will be a significant inflection point in the sales trajectory of Jardiance and the SGLT-2 inhibitor class as a whole - this would be much-welcome development given that management has acknowledged that sales for both Jardiance and the class as a whole did not experience as much of an upswing after the release of the EMPA-REG OUTCOME results as hoped. Management has also suggested that the other major inflection point in sales would be the inclusion of EMPA-REG OUTCOME findings in major diabetes treatment algorithms - we expect we may see more guidelines committees considering a more privileged position for empagliflozin following this label update.
- **Jardiance's label update bodes well for other diabetes drugs with demonstrated cardioprotective effects.** Novo Nordisk recently filed a Supplemental New Drug Application (sNDA) with the FDA and a Type II Variation application with the EMA, petitioning to include positive cardiovascular outcomes data from the LEADER trial on the label for GLP-1 agonist Victoza (liraglutide). It's unclear at this point if the FDA will require a dedicated Advisory Committee meeting to discuss a Victoza label update as it did for Jardiance, but we would love to see a second diabetes drug with a cardioprotective indication. CVOTs are a massive investment of time and resources, and label updates such as Jardiance's ensure that they produce as much value as possible.

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