CLOSER LOOK

MEMORANDUM

Zydus Cadila receives tentative FDA approval for generic DPP-4 inhibitor sitagliptin/metformin fixed-dose combination - July 11, 2017

Executive Highlights

- Zydus Cadila recently announced "tentative" FDA approval to market a generic fixed-dose combination of DPP-4 inhibitor sitagliptin/metformin (Merck's Janumet). As we understand it, this means that FDA is open to the possibility of marketing authorization prior to patent expiry - it does not necessarily mean that a generic version of Janumet will be available before the product's patents expire in 2022.
- Generic DPP-4 inhibitors would have a distinct positive impact on type 2 diabetes care, expanding access to this class of effective, safe, and well-tolerated agents. That said, DPP-4 inhibitors face increasing competitive pressure from SGLT-2 inhibitors and GLP-1 agonists. In all likelihood, this competition will only grow by 2022 as more CVOT data is published to support the CV benefits of these newer therapies (whereas in contrast, DPP-4 inhibitors have demonstrated CV safety but not cardioprotection).

Zydus Cadila announced recently that the India-based pharmaceutical company has received "tentative approval" from the FDA to market a generic fixed-dose combination of DPP-4 inhibitor sitagliptin/metformin (Merck's Janumet) in the US. Tentative approval indicates that the FDA is open to the possibility of marketing authorization prior to expiration of all patents on a branded product - 2022, in the case of Janumet. Per this recent development, Zydus Cadila may be able to sell its generic version in the US prior to that date, although nothing is yet final, and a high chance remains that Janumet will retain market exclusivity through 2022. That said, the first of Merck's patents on Januvia (sitagliptin) expired in April 2017, so generic DPP-4 inhibitors are right around the corner. Approval of Zydus Cadila's sitagliptin/metformin would introduce the first generic DPP-4 inhibitor product to the US market. Januvia is a market leader among DPP-4 inhibitors, capturing 61% of pooled class sales globally and >70% in the US in 1Q17. The class posted $9.7 billion in sales for the full year 2016, and the Januvia franchise was responsible for $6.1 billion. Januvia is the most profitable branded diabetes drug on the market, and we imagine a generic version of Janumet would meaningfully affect franchise sales. The availability of a generic DPP-4 inhibitor product will, of course (whether now or soon, within five years), greatly expand access, which will be positive for those recently-diagnosed in particular. Januvia, among other agents in the class, has demonstrated long-term safety and tolerability, which makes DPP-4 inhibitors the therapy of choice for older patients as well as those with renal impairment. The class boasts familiarity among diabetes care providers, despite increasing competition from SGLT-2 inhibitors and GLP-1 agonists, and we expect that a low-cost generic will increase the volume of DPP-4 products as well as the number of US patients taking them.

- **We spoke with Dr. Deepak Bhatt (Brigham and Women's Hospital, Boston, MA), who suggested that generic DPP-4 inhibitors could replace sulfonylureas in clinical practice.** Sulfonylurea treatment comes with substantial risk for hypoglycemia, weight gain, beta cell burnout, and potentially CV events, and yet agents in this class are commonly prescribed due to their generic status and low cost. As Dr. Robert Ratner shared at CMHC 2016, cost considerations are what keep sulfonylureas in play. A low-cost, generic DPP-4 agent might start to push sulfonylureas out of treatment algorithms - we're very excited by this prospect, as a safer, more effective generic class of diabetes therapy would improve outcomes for so many patients who currently face the roadblock of access/affordability. Dr. Bhatt described his personal perspective:

that if a generic DPP-4 inhibitor was available, he wouldn't turn to sulfonylureas given their uncharacterized CV risk.

- **On the other hand, Dr. Bhatt noted that the impact of a generic DPP-4 inhibitor product that enters the market in 2022 will at least partly depend on CVOT data for SGLT-2 inhibitors and GLP-1 agonists.** While CVOTs for DPP-4 inhibitors have largely shown CV safety vs. placebo (with the exception of a heart failure hospitalization signal found for saxagliptin and possibly alogliptin, but not sitagliptin), CVOTs are showing SGLT-2 and GLP-1 agents to be cardioprotective (EMPA-REG OUTCOME, CANVAS, LEADER). More of these large outcomes trials will report by 2022, which will markedly change the diabetes drug landscape, according to Dr. Bhatt. Competition from GLP-1 agonists and SGLT-2 inhibitors will only intensify as these newer therapy classes also become more familiar among diabetes care providers, with a longer record of safety/tolerability.

-- by Ann Carracher, Payal Marathe, and Kelly Close