CLOSER LOOK

MEMORANDUM

CVS Health and Express Scripts release 2018 formulary exclusions - August 5, 2017

Executive Highlights

- CVS Health has removed Lilly/BI's SGLT-2 inhibitor Jardiance from its 2018 formulary, adding J&J's Invokana back as a preferred drug.
- Express Scripts did not change its diabetes-related formulary for 2018. The PBM will continue to exclude Novo Nordisk's GLP-1 agonist Victoza in favor of Lilly's Trulicity and AZ's Bydureon and Byetta.
- Notably, CVS Health will launch a "Transform Obesity Value" initiative, tying obesity drug rebates to weight-based outcomes.
- In an interview with Dr. Thomas Seck, VP of Clinical Development and Medical Affairs at BI, we learned that Lilly/BI will collect more information on amputations in the ongoing EMPEROR HF (heart failure) and chronic kidney disease outcomes trials. Our sense is that it's hard to compare the Invokana and Jardiance CVOTs on the surface, because amputations were collected prospectively in CANVAS and retrospectively in EMPA-REG OUTCOME (notably, the FDA requested this method of data collection from J&J following an amputation signal seen in interim data), so we look forward to the additional safety data on empagliflozin.

Pharmacy benefits managers (PBMs) Express Scripts and CVS Health released their 2018 formularies earlier this week. The updated formularies will go into effect in January 2018. Most notably, CVS has newly-excluded Lilly/BI's SGLT-2 inhibitor Jardiance (empagliflozin) in favor of J&J's Invokana (canagliflozin) on its 2018 formulary. This exclusion applies to Synjardy (empagliflozin/metformin) and Synjardy XR (empagliflozin/metformin extended-release) as well, with Invokamet (canagliflozin/metformin) and Invokamet XR (canagliflozin/metformin extended-release) preferred. Previously, Invokana was excluded by CVS in 2016 and 2017. Although some have said the decision to bring it back is surprising in the aftermath of CANVAS results, we don't see it as surprising given our growing sense that heightened amputation risk associated with Invokana in very high-risk patients isn't likely to be viewed, ultimately, as associated with the molecule (this is conjecture from discussions with KOLs, and not proven yet). On the other hand, the clear, statistically significant reduced CV risk associated with Invokana would've given CVS greater confidence in the value associated with the drug from both glucose lowering as well as reduced CV risk perspectives. While CVOTs EMPA-REG OUTCOME (for empagliflozin) and CANVAS (for canagliflozin) showed that both agents confer near-equivalent risk reduction for CV events, the full CANVAS dataset presented in June at ADA 2017 also found a near-doubling of risk for lower limb amputations associated with Invokana. As a reminder, the FDA did issue a boxed warning for lower-extremity amputations on all canagliflozin-containing medicines in May whereas the EMA has the same for the class. Meanwhile, Lilly/BI released topline results from a pooled analysis of 19 empagliflozin studies, showing no imbalance in amputations or bone fractures between Jardiance vs. placebo groups - from our view, the studies are not comparable as the Lilly/BI trial was shorter and did not adjudicate the amputations in the same rigorous way, so we caution against direct comparison or over-interpretation of relative amputation risk. That said, in an interview with Dr. Thomas Seck (VP Clinical Development and Medical Affairs, BI), he noted that EMPA-REG OUTCOME investigators were not asked to collect amputation data prospectively because there was no safety signal in interim data. In contrast, an Independent Data Monitoring Committee (IDMC) for CANVAS asked for more rigorous data collection on this front. Notably, Jardiance carries an official indication for the reduction of CV death, and the product labels for Synjardy and Synjardy XR also include

the positive EMPA-REG OUTCOME data. While Invokana has no CV indication yet, J&J management shared plans to file a Supplemental New Drug Application (sNDA) requesting this by end of September.

Again, because many elements of trial design were different between the SGLT-2 inhibitor CVOTs, including how amputations were adjudicated (prospectively in CANVAS vs. retrospectively in EMPA-REG OUTCOME), the study population, and the length of trial, we're currently wary of over-comparing the two therapies based on these trials. But we'd also shy away from calling them interchangeable. At this point, we await further analyses of CANVAS that may help elucidate the amputation signal, or may reveal ways to manage the risk with proper patient selection, stronger education around foot care in diabetes, etc. Encouragingly, Dr. Seck shared that the EMPEROR HF (heart failure) and CKD outcomes trials will provide more detailed information on empagliflozin/amputations. He also pointed out that a clinical trial can never prove a negative - he has a point. Ultimately, an outcomes trial simultaneously studying multiple different SGLT-2 inhibitors would provide the best picture of these agents and their respective risks/benefits - in this environment, of course, we can't expect a major trial like this although it would be extremely instructive.

We expect the 2018 CVS Health formulary comes as very good news to J&J; we expect, of course, that the company's negotiations with the PBM around price/rebates came into play here. The Invokana franchise has been weak of late, with sales down 23% YOY in 2Q17 (US sales down a sizable 26%), and down 13% YOY in 1Q17 (US sales down 17%). As one of three major PBMs in the US (also Express Scripts and UnitedHealthcare), CVS Health manages coverage for 90 million Americans, though, as Dr. Seck pointed out, the Jardiance exclusion only applies to the CVS Health national formulary which determines coverage for a smaller group of ~25-27 million. Still, this change could be a big tailwind for Invokana in 2018, particularly considering the close competition between all three SGLT-2 inhibitors on the market this quarter. Jardiance experienced a particularly strong 2Q17, with revenue more than doubling YOY (albeit from a smaller base than Invokana sales). We'll be watching closely to see how this formulary change affects the SGLT-2 inhibitor market in 2018, and we'll be eager to hear commentary to this end from J&J, Lilly, and AZ management. To our knowledge, Express Scripts (which manages insurance plans for 83 million Americans) has no SGLT-2 inhibitor exclusions, with Invokana, Jardiance, and AZ's Farxiga (dapagliflozin) on equal footing. Farxiga will also retain its preferred status on the CVS Health formulary in 2018 (its positioning here is unaffected by the swap Jardiance/Invokana swap).

- **Turning to GLP-1 agonists: Express Scripts will continue to exclude Novo Nordisk's market-leading Victoza (liraglutide) as well as Sanofi's Adlyxin (lixisenatide) in 2018, favoring Lilly's Trulicity (dulaglutide) and AZ's Bydureon (exenatide once-weekly) and Byetta (exenatide once-daily). CVS has newly-excluded GSK's Tanzeum (albiglutide) on its 2018 formulary and will continue to exclude Bydureon and Byetta in favor of Victoza and Trulicity.** Express Scripts' continued exclusion of Victoza is notable for similar reasons as CVS' Jardiance exclusion: Victoza is the first product within the GLP-1 agonist class to demonstrate a cardioprotective benefit (in the LEADER trial), and an FDA advisory panel recently voted 17-2 in favor of approving a new CV indication for the drug (the EMA has already granted this indication for the reduction of CV events). Novo Nordisk has likely been limited in its ability to leverage the LEADER results in payer negotiations thus far, as the data is not yet included on the product label in any form. Still, we think it's unfortunate that the Express Scripts formulary restricts access to a known cardioprotective therapy in Victoza, especially since the alternative of Bydureon showed no CV benefit in EXSCEL, according to topline results from the CVOT (the REWIND trial for Trulicity is ongoing and expected to complete in July 2018) - we are eager to hear more at EASD, however, to understand how the compound looks - here again, differences in trial design, population, monitoring, etc could tell an interesting story. Despite this exclusion, Victoza captured an impressive 57% of the $1.4 billion GLP-1 agonist market in 1Q17, far ahead of its five in-class competitors. Tanzeum has been excluded from the Express Scripts formulary in the past, and CVS will follow suit in 2018. Notably, albiglutide has a comparatively weaker clinical profile vs. other GLP-1 agents, and GSK management recently announced plans to stop manufacturing Tanzeum and to "gradually" withdraw commercial support.

- **In 2018, CVS will introduce outcomes-based management to its obesity coverage as part of the "Transform Obesity Value" initiative.** CVS unveiled a set of new value-based initiatives aimed at better-aligning drug coverage with health outcomes. Obesity is one of three disease areas for which this program will be launched along with oncology and respiratory diseases. In obesity, this means a manufacturer will have to "provide additional value" (we imagine this means paying a higher rebate) if PBM members do not achieve a minimum level of weight loss within an initial assessment period. This announcement - while an exciting step forward in the movement toward value-based healthcare - is somewhat ambiguous and contains few details. We hope this program doesn't de-incentivize industry players from developing and marketing these agents. Obesity drugs are already underutilized due to high cost, poor reimbursement, stigma, and HCP reluctance to prescribe non-lifestyle interventions for weight loss (the market totaled just $122 million in 1Q17). It's unclear precisely how this change to reimbursement might affect the market, so we'll have to wait and observe - if anything, it actually sounds like access might be increased and CVS would simply not pay for the drugs if they didn't help people lose weight.
- **Neither CVS Health nor Express Scripts will change their positioning of basal insulin products in 2018.** In 2017, Lilly/BI's Basaglar (biosimilar insulin glargine) gained exclusive positioning over Sanofi's Lantus (insulin glargine) on the CVS Health and Unitedhealthcare formularies, and equal positioning to Lantus on Express Scripts - this all remains the same for 2018. In 2Q17, Lantus sales fell 18% YOY to $1.3 billion, following Basaglar's late 4Q16 launch in US pharmacies. On Sanofi's 2Q17 earnings call, management shared that the retention rate of patients on Lantus has been 50% so far within CVS Health and 56% within Unitedhealthcare, adding that the effect of formulary exclusion has only partially taken hold in 1H17 (the Unitedhealthcare formulary was only activated on April 1). Patient-switching to Basaglar is expected to accelerate in 2H17, and Sanofi management did not seem to expect any further changes to Lantus' formulary status in 2018. We look forward to hearing feedback from patients on this.
- **No changes to the CVS Health or Express Scripts formularies affect rapid-acting insulin products.** Express Scripts will continue to exclude Novo Nordisk's NovoLog (insulin aspart) and Sanofi's Apidra (insulin glulisine) in favor of Lilly's Humalog (insulin lispro). Novo Nordisk's human insulin Novolin is also excluded in favor Lilly's Humulin. The CVS formulary differs somewhat, with NovoLog preferred over Humalog and Apidra, and with Novolin preferred over Humulin. We'd like to get a better sense of when the formularies are forcing patients back onto "last-gen" insulin - we are worried that payers are missing the forest for the trees, saving some funds on older insulins vs. insulin analogs but losing funds on all the severe hypoglcyemia and DKA costs.
- **Formulary exclusions for DPP-4 inhibitors will remain the same in 2018.** Express Scripts will continue to exclude AZ's Onglyza (saxagliptin) and Takeda's Nesina (alogliptin) franchises in favor of Merck's Januvia (sitagliptin) and Lilly/BI's Tradjenta (linagliptin) franchises. CVS also prefers Januvia and Tradjenta over Onglyza and Nesina.
- **On the new therapy class of basal insulin/GLP-1 agonist combinations: Neither CVS Health nor Express Scripts have listed a preference for Sanofi's Soliqua (insulin glargine/lixisenatide) vs. Novo Nordisk's Xultophy (insulin degludec/liraglutide) but we have little idea of what hoops patients have to jump through to get either.** Both products were FDA-approved in November 2016. Sanofi swiftly launched Soliqua in US pharmacies shortly thereafter, in early January 2017, while Xultophy's US launch came in May 2017. In 1Q17, Xultophy hit $15 million in worldwide revenue, while Soliqua posted $4 million, up 25% sequentially to $6 million in 2Q17 - obviously the earlier launches internationally are helping Novo Nordisk relatively speaking. Notably, Sanofi has priced Soliqua (~$19.90/day) on par with other GLP-1 agonists (~$20-$25/day) in the US to help stimulate growth, while Novo Nordisk's strategy is to price Xultophy at a premium (~$31/day). These list prices are pre-rebate, and don't reflect differences due to dosing regimen. All this said, to be sure, it remains unclear how well-reimbursed this new class really is - our sense is that reimbursement could be far better and that doctors in the US could be much more open to trying combos first. US payers have historically required patients to

start on monotherapies before progressing to combination therapy, and this trend continues for fixed-ratio basal insulin/GLP-1 agonist products - this seems quite depressing given all the accolades given by KOLs, which have been largely ignored. HCPs in the US also seem reluctant to prescribe combo products early in the course of disease, before trying monotherapies first. In our view, these practices are counterintuitive to the benefit of these advanced formulations - namely, that being able to take a lower dose of each agent (the insulin and the GLP-1) minimizes side-effects while increasing efficacy and enhancing quality of life for patients, who face one co-pay instead of two, plus lower injection burden.

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