Closer Look

MEMORANDUM

German IQWiG finds "hint of minor added benefit" with GSK's Eperzan (albiglutide) - January 21, 2015

Executive Highlights

- A German government agency completed a competitive effectiveness analysis of GSK's once-weekly GLP-1 agonist Eperzan/Tanzeum (albiglutide), finding "hint of minor added benefit" vs. sulfonylureas for one of four pursued indications.
- This decision likely preserves GSK's ability to receive premium reimbursement for Eperzan in Germany; the same cannot be said for drugs that have received "no additional benefit" comparative efficacy rulings from the German government.

Shortly after the New Year, Germany's Institute for Quality and Efficiency in Health Care (IQWiG) published its assessment of GSK's once-weekly GLP-1 agonist albiglutide, which is marketed as Eperzan in the EU and Tanzeum in the US. IQWiG found a "hint of minor added benefit" (namely a reduction in hypoglycemia) with albiglutide vs. sulfonylureas when both were used on top of metformin. This represented one of four comparisons included in the assessment; IQWiG ruled that the data submitted was insufficient to address the other three indications. IQWiG assessments are used by the German Federal Joint Committee (G-BA) to negotiate on pricing with manufacturers.

"Hint of minor added benefit" may not sound like much of a win at first glance, but it represents (to our knowledge) the most positive IQWiG assessment of a GLP-1 agonist yet - a testament to how challenging IQWiG has been in diabetes. The agency found no added benefit with Sanofi's Lyxumia (lixisenatide) in 2013 (prompting the drug's withdrawal) and in 2007 ruled that the benefit of then-Lilly's Byetta (exenatide) was not yet proven. The agency does not yet appear to have published assessments on other drugs within the class, allowing them to stay on the market for now or at least until the G-BA decides to do a class-wide review. The dreaded "no additional benefit" generally relegates drugs to generic-level pricing. By our understanding, IQWiG's "hint of minor added benefit" ruling should be enough to preserve some degree of premium reimbursement for Eperzan in Germany, although nothing is known for certain until the G-BA releases its final decision.

- **The G-BA and IQWiG provide an extreme example of growing price pressure in the diabetes drug landscape as well as the disproportionate focus on acute vs. chronic conditions.** Germany's AMNOG was passed in 2010 in response to high and growing prices for prescription drugs. It outlined a system in which reimbursement would be tied to demonstration of a benefit vs. standard of care therapy. This turns out to be easier to prove for drugs for acute conditions (i.e.: cancer) than for drugs for chronic diseases such as diabetes. Even if IQWiG's analyses were based purely on clinical comparisons of therapies (which they are not always - see below), this means that diabetes drugs face more of an uphill battle. The pressure in Germany, Europe's largest market for medicines, contributes to the overall challenging reimbursement landscape and prospects for diabetes drug sales growth in Europe as a whole.
- **Unfortunately, most of IQWiG's negative rulings have been due to technicalities rather than balanced comparative efficacy assessments.** It is hard to argue that sulfonylureas or human insulin (the specified standard-of-care comparators for IQWiG's purposes) are the best therapies around, but the G-BA outlines a very strict set of requirements for the trials that can be used to support positive assessments. In nearly every analysis, IQWiG has found issue with trial design or the comparator therapy used in drugs' phase 3 programs. Some manufacturers

happened to conduct phase 3 trials that met the specifications, but most did not. This somewhat arbitrary evaluation system is, we imagine, highly frustrating for manufacturers as well as patients who begin treatment with a therapy that is subsequently withdrawn from the market. Manufacturers that receive negative rulings have the option to conduct additional studies and re-submit a dossier to IQWiG, but this is an expensive and involved process that many manufacturers decide is simply not worth it.

- **Interestingly, there has been less patient backlash to the withdrawal of diabetes therapy in Germany than might have been expected.** This may be partially due to the fact that most diabetes drug withdrawals (or non-launches) so far occurred in drug classes where alternative therapies are still reimbursed - the DPP-4 inhibitors are a prime example, where most drugs in the class have been withdrawn or were never launched but Merck's Januvia (sitagliptin) is still on the market.
    - **The lack of patient backlash may escalate, however, as IQWiG/G-BA rulings expanding to newer drugs.** The first two SGLT-2 inhibitors to market in Europe, J&J's Invokana (canagliflozin) and AZ's Forxiga (dapagliflozin) received negative G-BA rulings, causing both products to be withdrawn from the market. However, AZ was later able to re-negotiate on pricing and re-introduced Forxiga in Germany - we imagine at a significantly lower price. Some of the greatest pressure on the German government may stem from a decision on Novo Nordisk's ultra-long-acting basal insulin Tresiba (insulin degludec), which received a negative IQWiG ruling late last year. If the product ends up being withdrawn (which, to our knowledge, appears to be a distinct possibility), German patients will be deprived of one of the newest basal insulins, one that is available elsewhere in Europe. This may be particularly politically unpalatable given that Tresiba has demonstrated some if its greatest comparative benefit in pediatric diabetes patients.

-- by Manu Venkat and Kelly Close