Reimbursement at risk

Germany expands its review of diabetes therapies

Market analysts are forecasting that sales of diabetes drugs will continue to grow robustly over the next decade as the global diabetes epidemic continues to spiral out of control. Pharmaceutical manufacturers are stepping in to meet an unmet medical need and are launching innovative products worldwide, such as Boehringer Ingelheim and Eli Lilly's dipeptidyl peptidase-4 (DPP-4) inhibitor, Trajenta (linagliptin), for type 2 diabetes. In Europe, however, companies are facing growing uncertainty about whether the return on investment will be sufficient to make new product launches worthwhile there. This stems largely from new policies in Germany, a critical market that many other European countries follow when making their own pricing and reimbursement decisions.

Since the country's pharmaceutical market reform law, AMNOG, came into effect two years ago, its health technology assessment (HTA) and reimbursement decision-making bodies – the IQWiG and the G-BA, respectively – have taken an increasingly hard line when determining whether a new drug provides added value to patients compared with existing therapies. The result is that companies sometimes have to accept a non-negotiable reference price for their new products which can be equivalent to that of generics, or not market their drug in Germany at all.

> ***"It is an increasingly challenging market, especially in the diabetes sector."***
>
> *Neil Grubert*

Boehringer Ingelheim and Eli Lilly know better than most how challenging it can be to launch a new drug in the country, particularly in the competitive diabetes therapeutic area. In December 2012, the IQWiG for the second time concluded on a technicality that Trajenta offers patients no therapeutically significant additional benefits over comparator therapies on the market.[1] The IQWiG's justification was that the companies had not submitted any relevant studies.

The G-BA had asked for studies testing linagliptin against 'appropriate' comparators in three situations: monotherapy, dual therapy and triple therapy. According to the IQWiG, however, the companies had only submitted the results of placebo-controlled studies for mono and triple therapies, and had included data from a dual therapy study whose design was not relevant for the purpose of making an additional benefit determination. That study had tested the generic comparator glimepiride (a sulphonylurea) against linagliptin – each combined with the metformin – but the IQWiG deemed it unsuitable because it not only compared the two drugs with each other, but also compared two different treatment strategies.

For its part, Boehringer Ingelheim stands firmly behind its supporting evidence. "We were quite surprised that IQWiG questioned the scientific design of our study," company spokesman Arnd Prilipp told *MedNous*. "We provided IQWiG with study data comparing linagliptin in monotherapy and in dual (linagliptin+metformin) and triple combination (linagliptin+metformin+insulins) therapy," he added.

The IQWiG's second review of Trajenta follows a G-BA decision of 'no additional benefit' for the drug in March 2012. The original dossier was deemed incomplete because the companies had chosen a patented DPP-4 inhibitor as the comparator to Trajenta, rather than the generic sulphonylurea comparator therapy recommended by the G-BA. Under a special transitional rule, however, Boehringer Ingelheim and Eli Lilly – as well as others that found themselves in a similar situation – were allowed to resubmit new dossiers for reassessment up until the end of 2012. Trajenta was the first to be reassessed under this rule.

Boehringer Ingelheim and Eli Lilly have yet to launch Trajenta in Germany; ironically, they now find themselves in a position where they are producing the drug there for export to nearly 40 countries worldwide. "We are still very confident in Trajenta. We would love to bring it to the German market, but we've decided to wait for the final G-BA decision," said Mr Prilipp. He said that it was "too early to speculate what will happen if the G-BA makes a second 'no additional benefit' determination" in its final decision due at the end of February 2013.

Drugs that are determined to have 'no additional benefit' under an early benefit assessment are automatically placed in a non-negotiable reference price group. However, manufacturers of drugs that are considered to have an additional medical benefit (whether 'non-quantifiable', 'marginal', or 'considerable') may enter into pricing negotiations with the federal association of statutory health insurance (SHI) funds (GKV-Spitzenverband). The better the rating, the more leverage a company may have in these negotiations.

DPP-4 class under scrutiny

In light of the Trajenta review, the G-BA has decided to carry out a separate DPP-4 class assessment and has requested dossiers from all manufacturers of gliptins, ie Merck's Januvia (sitagliptin), Bristol-Myers Squibb and AstraZeneca's Onglyza (saxagliptin) and Novartis' Galvus (vildagliptin) – and their combinations with metformin. This is the first class assessment to take place under AMNOG, said Thomas Müller, head of the G-BA's Pharmaceuticals Department. (He noted that pre-AMNOG, the G-BA carried out a class assessment of all insulin analogues, but absent from this lengthy review were the requirement for dossiers and pricing negotiations.)

Dr Müller explained to *MedNous* that the drugs subject

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to the DPP-4 class assessment are already on the market in Germany, and the reason for the assessment is "to have a consistent assessment of all gliptins and to avoid distortion of competition between the gliptins". The six-month procedure is due to begin on 1 April 2013, after which any price negotiations with the GKV-Spitzenverband would take place over a further six months. Dr Müller did not rule out the possibility that the outcome of the G-BA's class assessment could be different from its imminent decision on Trajenta.

What does this mean for the diabetes sector?

Manufacturers of other new diabetes therapies will no doubt be wondering whether G-BA class assessments will become commonplace. For example, there may soon be a new glucagon-like peptide-1 receptor (GLP-1) agonist on the German market that could potentially trigger a class review of existing GLP-1 agonists. Sanofi's type 2 diabetes therapy Lyxumia (lixisenatide) received a positive opinion from the European Medicine Agency's Committee for Medicinal Products for Human Use (CHMP) in November 2012 and marketing approval by the European Commission on 4 February 2013. Although the company declined to comment on whether it plans to market the drug in Germany, the authorisation is valid across the EU.

There are currently three GLP-1 agonists on the German market: Novo Nordisk's Victoza (liraglutide) and Lilly Deutschland's Byetta and Bydureon (both exenatide). *MedNous* asked Dr Müller whether the G-BA anticipated a class assessment of GLP-1 agonists already on the market, to which he replied: "That is possible to avoid distortion of competition, but not yet decided." He also pointed out that the G-BA is "on the way to developing criteria to assess other drugs in the existing market. Until now, no list is available. We expect the next assessment out of the existing market starting in summer 2013".

Diabetes manufacturers will also be watching the G-BA's early benefit assessment of AstraZeneca and Bristol-Myers Squibb's Forxiga (dapagliflozin), a first-in-class therapy for the treatment of type 2 diabetes that works in the kidney to selectively inhibit sodium-glucose cotransporter 2 (SGLT2).[2] The drug was launched in Germany shortly after being granted an EU marketing authorisation in November 2012, and work has begun on its early benefit assessment.[3] A final G-BA decision on Forxiga is due by June 2013, Dr Müller confirmed.

Broader impact on the EU

Naturally, the most immediate impact of the G-BA's reimbursement decisions and the subsequent pricing determinations for diabetes therapies will be seen in Germany. "It is an increasingly challenging market, especially in the diabetes sector, which is very competitive," Neil Grubert, director of pricing and reimbursement research at the global consultancy Decision Resources told *MedNous*. Indeed, the company is in the process of reassessing an earlier forecast for the German market which had predicted that spending on type 2 diabetes therapies would increase from $1.5 billion in 2011 to $2.8 billion in 2021. The events in Germany "are slowing things down significantly," said the company's senior director of cardiovascular and metabolic disorders, Donny Wong, and as such, the new forecast will reflect this. He also pointed out that "the impact of even a 40% price reduction across the board for the DPP-IV inhibitors would diminish the market value of this drug class by over $400 million in Germany alone."

- **More than 55 million Europeans aged 20 to 79 have diabetes, with Germany ranking second in the number of reported cases.[4]**
- **By 2030, 64 million Europeans are expected to have the disease.[5]**
- **European expenditure on diabetes was nearly €139 billion in 2012.**

The effects of German pharmaceutical policies will be felt further afield, too. Edith Frénoy, director market access of the European Federation of Pharmaceutical Industries and Associations (EFPIA), says that industry is closely watching developments in the German pricing and reimbursement system "in general, [but] not limited to one therapeutic area…Because of the widespread use of international reference pricing in Europe, any decision to modify the price of pharmaceuticals marketed in Germany will automatically affect other European countries". She also noted that the German healthcare system "is potentially a model for many healthcare systems in evolution, within and also outside of Europe".

Though EFPIA feels that the early benefit assessments performed under AMNOG "are very conservative", Mrs Frénoy does not believe the G-BA's DPP-4 class assessment is the start of a new trend, and carrying out class reviews is certainly not unique to Germany. She told *MedNous*, however, that this type of review "would best look at all treatment options, rather than only pharmaceuticals…This would ensure that healthcare resources are efficiently spent across the system".

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This article was written by Karen Finn, contributing editor to *MedNous*.

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