PRICENTRIC® INSIGHTS:

Is BeNeLuxA Equipped for a Zolgensma Assessment?

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BENELUXA TAKES ON ZOLGENSMA

The BeNeLuxA initiative is set to take on Zolgensma (onasemnogene abeparvovec), an innovative gene therapy for children under two years old with spinal muscular atrophy (SMA), which was granted conditional approval for use in Europe in May.

Belgium, Ireland, and the Netherlands will undertake a joint health technology assessment (HTA) of Zolgensma as part of the application from AveXis, a Novartis company, with Austria serving as expert reviewer. The participating national HTA bodies are committed to aligning their timelines, methodology, and content of HTA processes, and after assessment, the countries will determine if they will enter joint price negotiations. However, whether Zolgensma will be reimbursed is up to the discretion of each country's relevant agency.

CROSS-BORDER COLLABORATION

The BeNeLuxA Initiative was initially formed in 2015 to promote cross-border collaboration in horizon scanning, information sharing, policy exchange, and HTA by Belgium and The Netherlands. That same year, Luxembourg joined the Initiative, followed by Austria in 2016 and Ireland most recently, in June 2018.

Through BeNeLuxA, participating countries are aiming to increase efficiency of the assessment and pricing and reimbursement of medicines by exchanging expertise, as well as by mutual recognition of HTAs. Importantly in Zolgensma's case, the group engages in joint price negotiations for specific products, in order to try and provide faster and broader patient access.

To date, the group has completed around 15 HTAs and has been most successful with pricing and reimbursement negotiations related to another SMA treatment, Biogen's Spinraza (nusinersen), which came about in July 2018. Following negotiations, Belgium and the Netherlands successfully reached an agreement on the reimbursement of Biogen's SMA treatment.

The confidential pricing agreement gives Biogen temporary reimbursement of the SMA drug until December 2020, on the condition that in the interim the company gathers real-world evidence (RWE) on safety, efficacy and use of Spinraza in clinical practice.

The interim entry agreement, which is the same in both Belgium and the Netherlands, demonstrated "a very clear and promising example of the benefits of working together on price negotiations and pharmaceutical policy," according to Bruno Bruins, the ex-Dutch Minister of Health, who hailed the relationship between Biogen and the Initiative as "a positive development."

Despite BeNeLuxA's success in negotiations with Biogen, Ireland's National Center for Pharmacoeconomics (NCPE) recommended against reimbursement of Spinraza because of the drug's price.

At the time, Biogen said in a statement: "Biogen provided the HSE with significant pricing proposal. Absolutely in line with the final price negotiated in countries aligned with Ireland in the BeNeLuxA initiative, which have each decided to reimburse Spinraza."

Eventually, Irish health regulators examined Spinraza once more after Biogen lowered its asking price and agreed to reimbursement.

Despite the initial issue with reimbursement in Ireland, the Spinraza triumph showed promise for the future of jointly assessing more expensive, innovative medicines – such as Zolgensma. Since BeNeLuxA is one of Europe's most mature cross-border collaborative initiatives, and has successfully negotiated access to Spinraza, the Initiative could serve as a test subject for the future of these types of collaborative efforts in Europe, which are not only becoming more common, but more empowered. The Nordics (Denmark, Finland, Iceland, Sweden, and Norway) recently announced their intention to enter joint negotiations with bluebird bio for Zynteglo (betibeglogene autotemcel), an evolution in their joint work from hospital medicine procurement by Denmark, Iceland, and Norway, and HTA by FiNoSe.

SPINRAZA/ZOLGENSMA PARALLELS

Zolgensma secured conditional approval from the European Medicines Agency (EMA) in May this year, joining Spinraza on the market. The latter SMA therapy was the first to gain approval from the European regulators via the accelerated assessment program, back in June 2017.

Both Spinraza and Zolgensma are first-of-their-kind SMA therapies with treatment costs that challenge the traditional payment expectations of European health systems. For reference, Spinraza costs around 600,000 euros in the first year and then around 300,000 euros each year thereafter, whereas the one-time treatment cost of Zolgensma costs nearly 2 million euros.

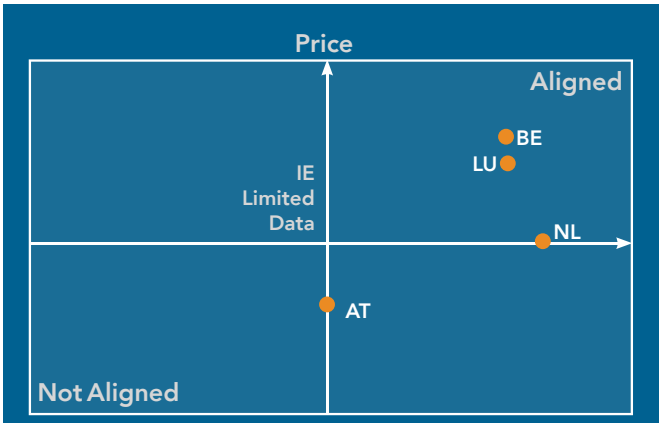
Both Spinraza and Zolgensma dramatically improve the lives of children with SMA and that of their caregivers, but they function in different ways. The latter is a gene therapy designed to replace the nonworking or missing SMN1 gene that causes the disorder, while Spinraza contains an antisense oligonucleotide that allows the body to produce more of a protein called survival motor neuron (SMN), a protein of which SMA patients do not produce enough.

The standout aspect of Zolgensma is that it is a one time, life-saving treatment to be given to patients under the age of two, consisting of a new, working copy of a human SMN gene delivered via a vector.

Novartis has previously expressed confidence that the one-time infusion gene therapy will essentially replace Spinraza as standard-of-care, following positive long-term data that showed significant therapeutic benefit in patients treated before symptoms arise, and sustained durability in patients up to five years post-dosing.

ALIGNMENT ISSUES

While BeNeLuxA is by far one of the most mature cross-border collaboration efforts, there are nonetheless pricing and reimbursement decision misalignments among participating countries. An inclusive European HTA and pricing negotiation environment offers a multitude of opportunities such as saving time and money, but if the countries cannot agree on various aspects of the process, primarily due to national-level idiosyncrasies, failures can occur.



Company	Distance	Language	Population (millions)	GDP/cap PPP (000s)
AT	Medium	N	8.9	47
BE	Short	Y	11.5	44
NL	Short	Y	17.3	50
LU	Short	Y	0.6	94
IE	Medium	N	4.8	70

Looking at drugs that have been assessed by the group in the past, common instances of HTA alignment occurred between the core three BeNeLuxA countries for AstraZeneca's Tagrisso (osimertinib), Pfizer's Vyndagel (tafamidis), and Ipsen's Xermelo (telotristat ethyl).

Specifically, across the 11 drugs that have been previously assessed, the Netherlands came to positive conclusions the most of all the countries, at 88% of the

time, followed by both Luxembourg and Belgium each at 75% of the time. Austria erred on the side of agreement 50% of the time, whereas Ireland joined too recently to draw any sound conclusions. However, as seen in the case of Spinraza, at the national level, Ireland deviated before ultimately deciding to back reimbursement.

With a total population of 43 million across the initiative, the core group of founding countries – Belgium, the Netherlands and Luxembourg – are seen to be more well aligned, with later entrants Ireland and Austria having less proven alignment or aligning their decisions less often.

The core three countries have more in common, which is conducive to them agreeing more often; on a basic level they share Dutch as a common official language and have the most similar cultures, on top of a stronger history of cooperation as a group and geographic closeness. Austria and Ireland were the most recent additions to the Initiative and Ireland has suffered from budget constraints and mismanagement, which have led it to promote more stringent reimbursement practices.

OTHER ISSUES

Joint decisions draw natural timeline comparisons to reimbursement and pricing differentials with non-joint decisions, as a core idea of syncing up practices is to expedite the time a drug takes to get to market.

Joint analysis can run into issues such as limited data, as well as being subject to variances in the specific product. EVERSANA data analysts found that, overall, submission through BeNeLuxA did not quicken the reimbursement timeline process for products approved in 2016 with costs > 50,000 EUR per annum; for example, in Belgium and the Netherlands there were products that secured reimbursement either more slowly or quickly than Spinraza.

However, among the BeNeLuxA countries, Austria and Ireland have trailed the Netherlands when it comes to reimbursing a medicine, and Belgium has trailed the Netherlands in time to reimbursement.

Price disagreements can also cause issues, such as when an earlier BeNeLuxA pilot for Vertex's Cystic Fibrosis (CF) medicine, Orkambi (lumacaftor/ivacaftor), failed to lead to a deal in 2016 and 2017 after the parties could not reach an agreement on an acceptable price. The Netherlands' Zorginstituut had advised at the time that a discount of 82% would be needed for Orkambi to be eligible for reimbursement.

In this instance, the BeNeLuxA countries seemed dead set on concluding an appropriate price for their constituents, especially given the access deals Vertex has been entering with payers for all current and future CF medicines. The Initiative does aim to strengthen negotiating power after all. The Netherlands now reimburses Orkambi, whereas Orkambi is a nonreimbursable medicine (under Category D) in Belgium, according to data from Pricentric.

LOOKING TO THE FUTURE OF JOINT HTA

The variance in success with BeNeLuxA in securing access to expensive, innovative medicines raises the question of whether the initiative represents the future of both market access and pricing and reimbursement negotiations.

Although Belgium, Ireland, and the Netherlands are aiming to align their HTA processes for Zolgensma, the negotiations for the reimbursement of the gene therapy in each market will most likely encounter some sort of strife due to the countries' idiosyncrasies, especially considering the limited data, given the novelty of Zolgensma. As seen before, the countries are not always

aligned in their decision-making, but looking at the Spinraza outcome, it can be assumed there will be collaboration and agreement among the core countries (BeNeLux).

As one of Europe's most mature cross-border initiatives, BeNeLuxA and its future success with negotiating access to innovative medicines could be indicative of cross-border collaboration as future standard protocol in Europe. As mentioned previously, in a similar vein, the Nordics are teaming up to negotiate access to Zynteglo, which signals a major shift in their policy. The initiative to jointly negotiate access to medicines is the next natural evolutionary step for these markets.

Likewise, the ten-country Valletta Declaration group announced towards the end of 2019 that it would be working to set up a framework to formulate more coherent pricing policies in regional markets and build trust around collective negotiations on regional prices for bulk purchases. Since then, there has been little action. But, in the future, it will be interesting to see how this plays out due to the varying sizes of the participating markets, as well as other barriers.

"As the trend of joint HTA assessment gains increased traction, it will be critical to thoughtfully assess potential impacts at the global level," said Max Kleitman, EVERSANA Senior Consultant. "The inherent conflict in trying to balance collective HTA assessment against individual countries' particular needs and resources presents a complex business challenge for companies for a number of reasons, including downstream IRP implications and launch sequencing considerations."

BeNeLuxA's success in joint negotiation suggests that when certain factors such as language and geography, as well as policy, are aligned, cross-border collaboration has the potential to hold the key to the future of market access.