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Access in all areas? a round up of developments in market access and health technology assessment: part 4

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In this latest update, we look at recent developments in market access including the pricing agreement of Libmeldy® by the Beneluxa Initiative, the financial impact of managed entry agreements in Italy and the restructuring of Agenzia Italiana del Farmaco (AIFA). We also highlight the collaboration between FINOSE and the New Expensive Drug (NED) section of the Nordic Pharmaceutical Forum.

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Variations in health technology assessment (HTA) methods and practices across countries have resulted in disparities in HTA outcomes and subsequent patient access to treatment [1,2]. Despite these differences, HTA processes often share common elements. When countries conduct these evaluations independently, it leads to unnecessary duplication of effort. International collaboration may help to address this issue; indeed, the forthcoming European Union (EU) HTA regulation seeks to promote the efficient use of HTA resources and minimize duplication [3]. While EU HTA primarily focuses on a joint clinical assessment, it has been recognized that cooperation beyond these domains, including economic evaluation and joint pricing negotiations, could be advantageous. In 2015, the Beneluxa Initiative was launched to explore such wider collaborative opportunities, such as joint HTA and price negotiations for pharmaceuticals [4]. The initiative brings together Belgium, The Netherlands, Luxembourg, Austria and Ireland, sharing the common goal of ensuring "*sustainable access to, and appropriate use of, medicines in the participating countries*". The Beneluxa Initiative aims to "*increase patients' access to high quality and affordable treatments*" by working together on topics of mutual interest while integrating joint processes within existing national procedures [5]. This approach potentially sets the Beneluxa Initiative apart from EU HTA, as assessments conducted within the Beneluxa framework automatically qualify as national assessments.

In January 2024, members of the Beneluxa Initiative announced that they had reached a mutually agreeable pricing arrangement with manufacturer Orchard Therapeutics for Libmeldy® (atidarsagene autotemcel), a therapy treating metachromatic leukodystrophy (MLD) [6]. Libmeldy is a gene therapy aiming to correct the underlying cause of MLD, a rare genetic neurometabolic disorder which leads to progressive loss of neurological function including the ability to move and communicate [7]. A joint HTA procedure for Libmeldy was initially performed by three of the Beneluxa countries, Ireland, Belgium and The Netherlands, in 2022 [8]. Following this, in 2023, the Beneluxa Initiative members stated they were unable to reach a price agreement with Orchard, partly because of the joint HTA highlighting uncertainty in long-term outcomes of patients due to limited follow-up data on patients taking Libmeldy [9]. The agreement announced this year arose from Orchard Therapeutics submitting additional longer-term follow-up data, reducing the uncertainty around cost–effectiveness of the treatment [10]. Orchard Therapeutics recently announced US launch plans for Lenmeldy™ (the US branding of Libmeldy) with a wholesale acquisition cost of US $4.25 million, making it the most expensive drug globally [7,11]. Notably however, the US Institute for Clinical and Economic Review (ICER) in their evaluation suggested that Lenmeldy would

be cost-effective up to a price of US $3.9 million, highlighting the tremendous benefits this treatment provides patients [12].

Libmeldy is the fourth drug assessed by the Beneluxa Initiative, and up next is Hemgenix® (etranacogene dezaparvovec) for hemophilia B [13]. Given well-known differences in HTA outcomes as noted earlier, it is perhaps surprising that the initiative has been able to successfully perform negotiations. This perhaps is because, historically, national recommendations have been remarkably similar between Beneluxa countries, likely reflecting similar processes, decision making values and priorities [14]. With the EU HTA regulation, it will be interesting to see how the Beneluxa Initiative joint negotiation can be integrated into an EU-wide joint clinical assessment framework. For manufacturers, the Beneluxa Initiative may offer a time-saving way of trying to secure reimbursement rather than trying to follow each country's individual processes.

Libmeldy was also assessed by the FINOSE collaboration in 2022 [15]. FINOSE is a joint HTA collaboration, which was initiated between the Finnish Medicines Agency (Fimea), the Norwegian Medicines Agency (NoMA) and the Swedish Dental and Pharmaceutical Benefits Agency (Tandvårds-och läkemedelsförmånsverke [TLV]), in 2017 with the Danish Medicines Council (DMC) joining in 2023 [16]. Joint assessments of pharmaceutical products by FINOSE involve evaluating relative effectiveness and cost–effectiveness to support decision-making processes by the individual countries. The four agencies collaborate on different tasks of the evaluation, leading to improved quality and efficiency, while aiming to reduce complexity, administrative burden and time to market for the pharmaceuticals [17]. The collaboration enables communication between the agencies during their normal HTA processes, with companies submitting simultaneously to all four agencies and signing a waiver to allow confidential communication between the agencies and decision-makers in each country. The FINOSE assessment of Libmeldy led to positive reimbursement in Norway, Sweden and Finland after the countries followed their own processes, as FINOSE only provides joint assessments and not joint reimbursement decision-making, unlike the Beneluxa Initiative. However, a collaboration between FINOSE and the NED (New Expensive Drug) section of the Nordic Pharmaceutical Forum was announced in February 2024 [18]. NED is a working group of the Nordic Pharmaceutical Forum consisting of the pricing negotiation authorities for Denmark, Norway, Iceland and Sweden [18]. When a new FINOSE assessment is to be initiated, FINOSE will inform NED if the manufacturer is interested in joint price negotiations, and NED will assess whether the product is suitable for a joint negotiation [19]. The decision to undertake a joint Nordic price negotiation is between NED and the manufacturer – it is not a requirement that all drugs jointly assessed by FINOSE should go through a joint negotiation and conversely drugs going through a joint negotiation do not need to have undergone a FINOSE assessment. Nevertheless, the collaboration between FINOSE and NED aims to promote quicker and more equal patient access across these countries, similar to the Beneluxa Initiative [18].

Managed entry agreements (MEAs) are arrangements between a manufacturer and payer that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These agreements aim to facilitate patient access to innovative treatments while managing uncertainties and ensuring the sustainability of healthcare systems. MEAs can be broadly categorized into two main types: finance-based agreements and performance/outcome-based agreements, with some arrangements combining elements of both. Finance-based MEAs focus on containing costs and improving the affordability of a product. These agreements may include price/volume caps and confidential discounts. Performance/outcome-based MEAs aim to reduce uncertainties surrounding the therapeutic value of a drug by tying reimbursement to patient health outcomes. By employing MEAs, healthcare systems can manage the introduction of new health technologies while addressing concerns about their effectiveness, cost–effectiveness and budget impact. Many countries have implemented MEAs including the UK, Italy, Switzerland, France and Australia [20]. Italy was one of the first countries to use an MEA, with the Agenzia Italiana del Farmaco (AIFA) agreeing on its first contract in 2006 [21]. However, despite the increasing use of MEAs over time, it is not clear whether they financially benefit the health system implementing them. A recent study by Trotta *et al.* [21], found limited evidence of MEAs lowering pharmaceutical expenditure in Italy in 2019–2021. Of 62 medications with MEAs analyzed, 39% had financial-based MEAs, 48% outcome-based MEAs, and 13% mixed MEAs [21]. Over the 3 years of the study, there was a total payback amount of €327.5 million corresponding to 0.9% of the €41.1 billion total public expenditure on medications in Italy [21]. The largest share of paybacks (€158.1 million), came from financial-based MEAs, whereas the outcome-based MEAs generated €74.5 million in paybacks [21]. The median payback was 3.8% of the expenditure for each of the medications included in the sample [21]. The work of Trotta and colleagues supports the general body of evidence that MEAs may be more effective in ensuring access to innovative treatments and promoting their optimal use rather than guaranteeing

the sustainability of pharmaceutical expenditure. Trotta *et al.* suggest that payers should consider several factors before implementing MEAs including the administrative burden required for implementing MEAs (which includes developing and maintaining patient registries and can be substantial), the outcomes to be used in performance based MEAs, and the duration of any MEA [21]. Whether these findings will influence the future implementation of MEAs by AIFA remains to be seen.

AIFA itself has initiated a major reorganization, effective from January 2024 [22]. The primary objective of the restructure is to expedite drug approval processes, ultimately ensuring that the Italian population has swift access to the latest medical innovations. One of the key changes is the creation of the 'Scientific and Economic Commission for Medicines', which will replace both the Technical and Scientific Committee (CTS) and the Pricing and Reimbursement Committee (CPR) [23]. The CTS has historically evaluated medicinal products from a clinical point of view, making a binding opinion on the therapeutic value of the medicinal product. After the CTS evaluation, the CPR then normally negotiates with pharmaceutical companies to set prices (including negotiating MEAs). The new Scientific and Economic commission will now undertake both value assessments and pricing/reimbursement negotiations [22,23]. This consolidation will result in a reduction of the number of members involved in drug assessment from twenty to ten [22]. The reduction in personnel has raised concerns given the additional work that will be required to align AIFA with the EU HTA regulation, although fewer people involved may offer a more agile approach to decision making. As the restructuring takes effect, stakeholders will be closely monitoring its impact on medicine reimbursement. The success of the changes at AIFA will be measured by its ability to bring innovative medicines to Italian patients more quickly, a target that both manufacturers and patients hope will be achieved.

Preparations for EU HTA were highlighted in TLV's annual report for 2023, which noted the TLV had invested significant time and resources into getting ready for the new HTA regulation [24]. This included national preparatory work to adapt Swedish process to align with processes at the EU level, despite receiving no additional resources to undertake this [24]. They note that the TLV will need to produce PICOs for all products processed by the EMA, which will be more than the number of treatments TLV receives applications for currently [24]. The TLV will also need to include statements from clinical experts which requires collaboration at a regional level [24]. There will also be a need for enhancement of skills in the TLV to prepare for new tasks demanded by the EU HTA process [24]. As the TLV note in their report, the extent to which countries can benefit from the joint assessments will depend on how well countries' national processes are aligned with the EU HTA [25], and whether they can therefore avoid having to repeat assessment steps. Regardless, joint clinical assessments cover only a relatively small portion of the assessment work undertaken by national HTA agencies, and they will still have to do much of the work they do currently to ultimately make reimbursement decisions about new drugs.

In conclusion, recent developments highlight the growing trend toward international collaboration and the potential benefits of such initiatives. The restructuring of AIFA and the preparations undertaken by TLV for EU HTA underscore the continually evolving HTA landscape. As countries continue to explore collaborative approaches to HTA and market access, it will be crucial to ensure they ultimately lead to the improvements they seek: faster and broader patient access to medicines.

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References

1. Jenei K, Raymakers AJN, Bayle A *et al.* Health technology assessment for cancer medicines across the G7 countries and Oceania: an international, cross-sectional study. *Lancet Oncol.* 24(6), 624–635 (2023).
2. Gilardino R, Treharne C, Mardiguian S, Ramagopalan SV. Access in all areas? A round up of developments in market access and health technology assessment: part 1. *J. Comp. Eff. Res.* 12(10), e230129 (2023).
3. European Commission. Regulation on Health Technology Assessment (2024). Available at: https://health.ec.europa.eu/health-technology-assessment/regulation-health-technology-assessment_en
4. Beneluxa Initiative. Available at: https://beneluxa.org/collaboration
5. Beneluxa Initiative. About Beneluxa – statements (2021). Available at: https://beneluxa.org/statements
6. Beneluxa Initiative. Beneluxa Initiative announces successful conclusion of Libmeldy price negotiations, directly benefiting patients in three countries (2021). Available at: https://beneluxa.org/news1
7. Orchard Therapeutics. Orchard Therapeutics Outlines U.S. Launch Plans for Lenmeldy™ (atidarsagene autotemcel), the Only Approved Therapy for Children with Early-onset Metachromatic Leukodystrophy | Orchard Therapeutics (2024). Available at: https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-outlines-us-launch-plans-lenmeldytm/
8. Ministerie van Volksgezondheid Welzijn en Sport. Pakketadvies sluisgeneesmiddel atidarsagene autotemcel (Libmeldy®) voor de behandeling van metachromatische leukodystrofie (MLD) – Advies – Zorginstituut Nederland (2024). Available at: https://www.zorginstituutnederland.nl/publicaties/adviezen/2022/09/27/pakketadvies-sluisgeneesmiddel-atidarsagene-autotemcel-libmeldy
9. Ministerie van Volksgezondheid Welzijn en Sport. Geneesmiddel Libmeldy niet in verzekerd pakket (2023). Available at: https://www.rijksoverheid.nl/actueel/nieuws/2023/04/12/geneesmiddel-libmeldy-niet-in-verzekerd-pakket
10. Orchard Therapeutic. Orchard Therapeutics Announces Agreement with the Beneluxa Consortium Enabling Reimbursed Access to Libmeldy (2024). Available at: https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-announces-agreement-beneluxa-consortium/
11. Oliver Barnes. Rare genetic disease therapy becomes world's most expensive drug at $4.25 mn (2024). Available at: https://www.ft.com/content/6678c805-6a70-488c-a48e-97813c8778b5
12. ICER. Atidarsagene Autotemcel for Metachromatic Leukodystrophy (2023). Available at: https://icer.org/wp-content/uploads/2023/10/MLD-Final-Evidence-Report_For-Publication_10302023.pdf
13. Beneluxa Initiative. Archive BeNeLuxA (2023). Available at: https://beneluxa.org/archive#toc-27-october-2023-joint-health-technology-assessment-for-hemgenix
14. Vreman RA, van Hoof D, Nachtnebel A *et al.* The Beneluxa Initiative domain task force health technology assessment: a comparison of member countries' past health technology assessments. *Int. J. Tech. Assess. Health Care* 39(1), e44 (2023).
15. Tandvårds-och läkemedelsförmånsverket TLV. Health economic assessment of the gene therapy Libmeldy in metachromatic leukodystrophy (2022). Available at: https://www.tlv.se/publikationer/publikationer/2022-02-21-halsoekonomisk-bedomning-av-genterapin-libmeldy-vid-metakromatisk-leukodystrofi.html
16. FINOSE. FINOSE collaboration prolonged and strengthened by entry of the Danish Medicines Council (2023). Available at: https://www.dmp.no/en/news/finose-collaboration-prolonged-and-strengthened-by-entry-of-the-danish-medicines-council
17. FINOSE. FINOSE (2023). Available at: https://www.dmp.no/en/public-funding-and-pricing-of-medicines/single-technology-assessments/finose
18. FINOSE. Collaboration with Nordic Pharmaceutical Forum (2024). Available at: https://www.dmp.no/en/public-funding-and-pricing-of-medicines/single-technology-assessments/finose/collaboration-with-nordic-pharmaceutical-forum
19. FINOSE. Description of the collaboration between FINOSE and New Expensive Drugs (NED) in the process for new drugs going through FINOSE HTA and joint Nordic negotiations (2024). Available at: https://www.dmp.no/globalassets/documents/english/public-funding-and-pricing/finose/process-finose---ndl-2024-01-31.pdf
20. Vokinger KN. Do managed entry agreements contribute to lower pharmaceutical spending? *AMA Health Forum* 4(12), e234610 (2023).
21. Trotta F, Guerrizio MA, Di Filippo A, Cangini A. Financial outcomes of managed entry agreements for pharmaceuticals in Italy. *JAMA Health Forum* 4(12), e234611 (2023).
22. Monni S. AIFA reform: what is it and who are the members of the governance (2024). Available at: https://safetydrugs.it/en/aifa-reform/
23. AIFA. Scientific and Economic Committee for Medicines (2024). Available at: https://www.aifa.gov.it/commissione-scientifica-economica

24. Tandvårds-och läkemedelsförmånsverket TLV. Årsredovisning 2023: beredskapsfrågor och uppdaterad värdebaserad prissättning i fokus (2024). Available at: https://www.tlv.se/press/nyheter/arkiv/2024-02-22-arsredovisning-2023-beredskapsfragor-och-uppdaterad-vardebaserad-prissattning-i-fokus.html

25. Tandvårds-och läkemedelsförmånsverket TLV. Årsredovisning 2023. Available at: https://www.tlv.se/download/18.337aa4e18d827bd2b7ac521/1708612710349/arsredovisning_tlv_2023.pdf (2024).

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