Future BeNeLuxAI Success – a Partnership Vs a Prescription Model

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BeNeLuxAI

*The BeNeLuxAI initiative was formed during the informal meeting of European Ministers for Employment, Social Policy, Health and Consumer Affairs in Riga, Latvia, in **April 2015,** where the health ministers of Belgium & the Netherlands announced a collaboration on pharmaceutical policy. The following countries then joined the initiative: Luxembourg (2015), Austria (2016) and Ireland (2018). The collaborative procedure fits into the national procedures & timelines required by the Transparency directive (89/105/EEC). Common activities include Horizon scanning, Information sharing, HTA , pricing and reimbursement.*

01 OBJECTIVES:

Since 2015 there has been substantial growth in multi-country collaborations across Europe (Visegrad Group, Valletta Declaration etc.), driven by the increasing number of expensive innovative drugs with unmet medical need. By joining together, countries increase the efficiency of their health technology assessment (HTA) processes to achieve greater bargaining power during price negotiations and ensure patients have timely access to affordable medications. BeNeLuxAI brings together Belgium, The Netherlands, Luxembourg, Austria and Ireland with a combined total population of 43 million. Pharmaceutical companies are unlikely to enter into joint processes without clarity on the assessment pathway including the methods and the decision criteria to be applied. Orphan medicinal products or advanced therapy medicinal products (ATMPs) for which market access in the individual countries is particularly challenging and time consuming, would benefit from a joint economic assessment. The objective of this study is to analyse existing HTA and reimbursement procedures within BeNeLuxAI partner countries and draw out some of the key issues for further debate.

02 Methods

The study sought to highlight the differences in methodological approaches of the HTA submissions, decision criteria, and timelines to patient access.

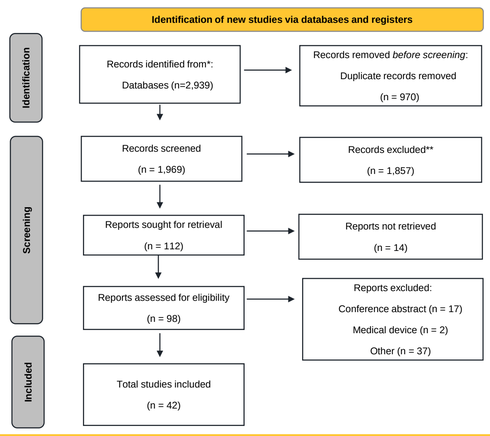
A comprehensive literature review was undertaken for all publications from 2000 to 21st of September 2022 using PubMed, Medline, EMBASE, & Google Scholar databases.

Studies were eligible for inclusion if they reported “Methods” AND “cost effectiveness studies” OR “Health Technology Assessment” OR “Methodological Guideline” OR “Methodological Manual” of the countries in question. Luxembourg is not included as it does not have n independent HTA assessment body.

The database searches yielded 2,939 articles; the article disposition is presented in Figure 1.

Of the 34 eligible articles; 34 provided information on methodological approaches of the HTA submissions of the BeNeLuxAI countries, 3 on timelines to patient access and 5 on the BeNeLuxAI initiative in general.

Figure 1: PRISMA flow diagram of SLR



03 Results

The proposed advantage of collective action amongst small countries to negotiate collectively to achieve a better price seems at least in theory to make sense, but it is worth considering the technical framework behind this in greater detail. For BeNeLuxAI member countries to negotiate collectively on a common drug price, the following critical questions arise:

- What is an acceptable common price given the current differences in HTA processes and price levels among BeNeLuxAI members? E.g. consideration on different internal and external reference legislation for maximum prices and reimbursement levels. Does the outcome of the negotiations really need to lead to a common price?
- What is the right timing to submit a dossier for joint submission and commence the joint negotiations?
- Could a joint process delay the market launch in one or more individual BeNeLuxAI countries and delays the access to these patients?
- Is a joint process associated with a higher possibility of reimbursement and/or lower price discount than a national process?

Reimbursement Systems

Policymakers face important challenges when implementing pharmaceutical policies that aim to achieve affordable, equitable and, at the same time, sustainable access to medicines. Reimbursement systems of BeNeLuxAI members face the largest differences in the following aspects:

- In all countries except Austria, reimbursement procedures apply to both the inpatient and the outpatient setting, carried out by the same agency. For hospital products In Austria there is no standardised HTA process.

Relevant commonalities are:

- All BeNeLuxAI countries have an external reference pricing (ERP) model in use. In Austria ERP is also used in the field of innovative medicines as the reimbursement price must not exceed the EU average price while in Ireland the maximum price allowable is the average of 13 EU countries plus the UK
- The evaluation process of a drug to seek reimbursement is initiated with an application submitted by the marketing authorisation holder in all BeNeLuxAI countries.

Table 1 shows key components to the various reimbursement systems of the countries in BeNeLuxAI.

Table1: Reimbursement Systems of individual BeNeLuxAI member countries

	Austria	Belgium	Netherlands	Ireland
Reimbursement Agency	Main Association of Austrian Social Security Institutions*	National Institute for Health and Disability Insurance (RIZIV/INAMI)	National Health Care Institute (ZIN)	National Centre for Pharmacoeconomics (NCPE)
Positive list	'Erstattungskodex , EKO)' (Reimbursement Code)	Positive reimbusement list system	Outpatient: list 1B Inpatient: 1) hospital budget 2) add-on list for expensive drugs based on budget criteria	Published reimbursement List
HTA process implemented	√ for innovative pharmaceuticals of the outpatient setting	1) for class A products 2) No difference between in-patienta and outpatient	1) outpatient: list 1B 2) inpatient: add-on candidates in lock	Full HTA for many High cost drugs including those for Oncology & Orphan indications as well as ATMP's
Same Reimbursement /HTA process for the in- and outpatient setting	No	Yes	1) HTA is similar 2 Need HTA differs for inpatient (add-on) and outpatient (list 1B)	Yes
External Reference pricing	EU-26 average price as price cap	EU-26 focus on France, Netherlands, Germany, Ireland, Austria, & Finland	Belgium, France, UK, and Norway,	Average of EU 13 + UK maximum price possible
Internal reference pricing	Yes	Yes	Yes	Yes
MEA	Cost- and risk-sharing models; no performance-based MEAs	Price volume arrangements	especially pay-for - performance for orphan drugs	Various models exist under HSE and Medicine Management Programme (MMP)
Specific funding models for high-cost medicines	Yes §15a Agreement on the Organisation and Financing of Health Care	N.A.	Special arrangements	Yes High Tech Drugs (HTD), Oncology Drug Management System (ODMS) & National Drugs Management Scheme (NDMS)

* responsible for the outpatient setting

MEA: Include Finance-based Agreements (FBAs) and Performance-based Agreements (PBAs)

FBAs are characterized by their aim to contain costs and facilitate the affordability of a product on the market by also including the manufacturer on the financing of a product.

PBAs seek to reduce uncertainties surrounding the effectiveness of a product by holding manufacturers accountable for their outcomes in the real-world post approval. (Definition from Dabbous et al. VALUE HEALTH. 2020; 23(4):425–433

Timing

Collaborative HTAs must be timely to reflect national decision-making priorities and to fit into any other steps of the procedures that the HTA or evaluation of the company submission is informing.

Research on availability of new medicines is routinely published by EFPIA with the “time to availability” data reflecting the number of days between marketing authorisation and the point at which products gain access to the reimbursement list.

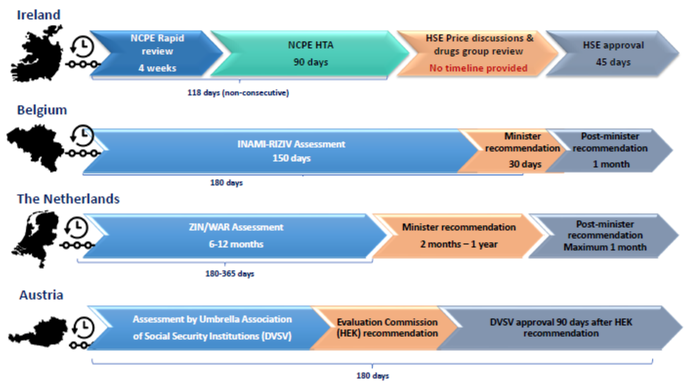
There is an important limitation to this dataset which arises from the fact that companies do not always apply for reimbursement at the date of a marketing authorisation is granted ; indeed country launch sequencing plans are a factor in delayed timelines to official listing on public reimbursement lists .

The most recent data from EFPIA report of July 2022 for the period 2017-2020 show that

- For Austria the average time from market authorisation to reimbursement is 315 days based on 127 products
- In Belgium the number of days is 534
- In the Netherlands the number of days is 294 days
- In Ireland the total number of days is 541 days.

The timelines on official assessment to published decisions on reimbursement for each individual member country of BeNeLuxAI is shown in Figure 2 below.

Figure 2: Official timelines of BeNeluxAI individual member countries



The four agencies in the BeNeLuxAI countries have previously advised of their commitment to align on assessment timelines. If the procedure times are based on the country with the fastest reimbursement procedures, countries such as Belgium or Ireland would potentially benefit from a joint HTA. According to the results from the SLR conducted though overall, submissions through the BeNeLuxAI route did not quicken the reimbursement timeline process for products approved in 2016 with costs > 50,000 € per annum.

The European Commission is currently preparing a revision of the EU Pharmaceutical Legislation and has put forward a range of proposals to address patient access inequalities across EU member states. Joint HTA (on EU level or other country collaborations) can help to standardise patient access to innovative products with medical need.

Methodological approaches of HTA

The evaluation of the results of the SLR shows considerable differences in the methodological approach. The study identifies differences in perspective, cost-effectiveness-thresholds, discount rates for costs and outcomes amongst the members of BeNeLuxAI.

The question of methods divergence is a relevant issue when HTAs were re-used by another BeNeLuxAI member (see table 3). Current BeNeLuxAI documents indicate that mutual HTA recognition may involve one country adopting parts or all of an HTA conducted by another member country. We have learned in the past that economic evaluations require local data and analyses customised for each setting. Full mutual recognition may lead to opposing conclusions on the cost effectiveness of the same interventions.

A fundamental part of the HTA decision framework is the use of cost-effectiveness thresholds. Ireland is the only BeNeLuxAI member that has previously advised a clear threshold, currently between €20,000 and €45,000 per quality-adjusted life-year (QALY). The Dutch do not employ a single threshold but suggest a wide range of €20,000–80,000 per QALY, depending on disease severity. For Belgium there is no formal threshold bur acceptable ranges vary from 30,000 to 60,000. In addition, the weight of budget impact seems higher than the incremental cost-effectiveness ratio in Belgium.

The BeNeLuxAI initiative do recognise there are methodological differences between member countries and the Applicant Submission Template recommends: *“for the different countries it would be useful to set the model with a front interface allowing choice of country to automatically change the parameters e.g. discounting, utility etc. One model is preferred, incorporating all countries.”(file:///C:/Users/ew/ipf-ac.at/Publikationen%20-%20Dokumente/Poster%20ISPOR%202022/Abstracts/BeNeLuxAI/Literatur/BeNeLuxAI_Applicant_Template.pdf)*

HTA methods develop over time, hopefully through a thoughtful process of debate. One way to achieve a more uniform approach would be the joint initiative within the framework of the EU HTA.

Table 2 reflects the key differences in methods used in Economic evaluations across the countries of the BeNeLuxAI initiative

Table 2: Methodological approach to the evaluation of innovative medicinal products

Parameter	Austria	Belgium	Netherlands	Ireland
Evaluation criteria of the HTA procedure:	Severity of the disease, unmet need, therapeutic added value	Therapeutic added benefit, budget impact, importance in clinical practice	Therapeutic added value, data quality (GRADE criteria).	Therapeutic added benefit, cost-effectiveness, budget impact, risks, unmet need
Mortality	√	√	√	√
Morbidity	√	√	√	√
Years of life gained	√	√	√	√
Safety & Adverse Events	√	√	√	√
Quality of life	√ (EQ-5D)	√ (EQ-5D, in exceptional cases TTO, SG)	√ (EQ-5D)	√ (EQ-5D, SF-6D)
Surrogate parameters	considered	considered	considered	considered
Conditions for pharmaco-economic studies	Pharmacoeconomic analyses are mandatory for medicinal products with claimed substantial, additional therapeutic benefits in the outpatient setting	Pharmacoeconomic analyses are mandatory.	Pharmacological analyses: necessary if the expected budget impact ≥ € 2.5 million p.a. and with appropriate data security for clinical efficacy (depending on the rarity and severity of the disease). For an ICER ≥ 25,000 € / QALY, a formal HTA is necessary.	Pharmacoeconomic analyses are mandatory
Innovation degree	√ (substantial, additional therapeutic benefit)	√ (Class I-III)	√	Not formally recognised
Guidelines for pharmaco-economic studies	√	√	√	√
Cost	Direct cost	Direct costs (non-healthcare costs can be reported in a separate analysis).	Social perspective – non-intervention-associated medical costs must be reported separately.	Direct cost
Study design	CEA, CUA	CEA/CUA, BIA mandatory	CUA	CUA, alternatively CEA if justifiable
Perspective	Health care system perspective	Payer perspective (RIZIV/INAMI +patient)	Society perspective	Cost: Health care system perspective Outcomes: Patient level
Comparators	Standard therapy, BSC, off-label therapy	All relevant treatments for the target indication /population, without dominated or extensively dominated interventions. Off-label products should only be used if clinical safety and efficacy are demonstrated.	Standard of care or routine therapy in the Netherlands	Standard of care / routine clinical therapies
Discount rate costs	3%	3%	4%	4%
Discount rate Outcomes	3%	1,5%	1,5%	4%
Time horizon	Depending on the form of analysis and the course of the disease. The examination period should be sufficient for treatment results to be taken into account.	The time horizon should be able to reflect the main differences in costs and outcomes.	CUA: Lifetime, BIM: ≥ 3 years	Lifretime : sufficiently long to capture all relevant differences in future costs and results
ICER thresholds	N/A	N/A	N/A (80,000/QALY at high disease burden)	€20,000/QALY and €45,000/QALY
Budget Impact Analysis	√ (optional)	√	√	√
Sensitivity analysis	√	√ (PSA recommended for CEA)	√ (DSA, PSA and scenario analysis)	√ (DSA, PSA)

Examples from the assessment carried

The BeNeLuxAI Initiative reported that motivating the pharmaceutical industry (particularly large multinational companies) to enter into negotiations with the collaborative has proved difficult. Additional challenges will arise with differences between the member countries in national pricing and reimbursement processes, and different health economic guidelines especially on perspective used for decision making.

A number of drugs have been evaluated by the group in the past including Tagrisso (osimertinib) from AstraZeneca (Vyndagel (tafamidis) from Pfizer and Xermelo (telotristat-ethyl) from Ipsen and HTA alignment occurred (Eversana 2020). Among the 11 drugs previously assessed, the Netherlands came to the most positive conclusions of all countries, with 88% of cases, followed by Luxembourg and Belgium with 75% of each. Austria erred in 50% of cases on the side of agreement, while Ireland, as the most recent country to join having only limited experience to draw upon. Of note though with Spinraza, at the national level, Ireland deviated before ultimately deciding to back reimbursement (Eversana 2020).

Table 3 outlines past collaborations of countries in the BeNeLuxAI initiative

Branded Name	Approval Date	Company	Therapeutic Area	Year	HTA Type
Lojuxta	2013	Aegerion	Hyper-cholesterolemia	2015	Belgium re-used the Dutch HTA
Orkambi	2015	Verex	Cystic-fibrosis	2016	1st submission – joint HTA (Belgium and Netherlands); external referee (Dutch Zorginstituut); Luxembourg used final report
Praluent	2015	Sanofi	Dyslipidemia	2016	External referee (Dutch Zorginstituut for Belgium)
Orkambi	2015	Verex	Cystic-fibrosis	2017	2nd submission – joint HTA (Belgium and Netherlands); external referee (Dutch Zorginstituut); final report sent to Luxembourg and Austria
Vydaqel	2011	Pfizer	Amyloidosis	2017	External referee (Dutch Zorginstituut); Luxembourg used final report
Rydapt	2017	Novartis	Acute Leukaemia	2018	Belgium re-used EUnetHTA
Ocaliva	2016	Intercept	Primary billary cholangitis	2018	Joint HTA (Belgium and Netherlands)
Spinraza	2017	Biogen	Spinale Muscular Atrophy	2018	Joint HTA (Belgium and Netherlands)
Xermelo	2017	Serb SAS	Carcinoid syndrome	2018	Belgium re-used Dutch HTA
Ravicti	2015	Immedica Pharma	Urea cycle disorder	2018	Belgium re-used Dutch HTA
Tagrisso	2016	AstraZeneca	1st line NSC lung cancer	2018	Belgium re-used Austrian HTA
Alecensa	2017	Roche	First line ALK+ lung cancer	2018	Austria re-used EUnetHTA
Zolgensma	2019	Novartis	SpinalMuscular Atrophy	2021	Belgium, Ireland and the Netherlands reached an agreement on the pricing of Zolgensma which will be reimbursed for two specific groups of young patients in all three countries.
Libmeldy	2020	Orchard Therapeutics	Metachromatic Leukodystrophy	2022	Ireland, Belgium and the Netherlands with Joint HTA conducted by NCPE ZIN, Amsterdam, contributed as co-author and DSV, Vienna, as reviewer.

04 Conclusions

A value-chain perspective is being adopted by the BeNeLuxAI Initiative which effectively involves the monitoring of medicines during: (1) pre-launch research and development; (2) the peri-launch period after marketing authorisation and before launch onto the market (pricing and reimbursement decisions); and (3) the post-launch period where measures can be taken to promote the appropriate prescription, supply and use of medicinal products (Vogler et al. 2021). In addition to joint price negotiations, the BeNeLuxAI initiative has collaborated on Horizon Scanning and Health Technology Assessment, leading to the alignment of health technology assessment timelines and methodologies within the collaboration. Furthermore, a common template has been created to help manufacturers submit dossiers for joint assessments (Vogler et al. 2021).

Our view is that suitable products for joint submissions at BeNeLuxAI would be pharmaceuticals with (high) unmet medical need, expected added value and a satisfactory degree of evidence. A successful joint negotiation amongst a cluster such as BeNeluxAI, does not necessarily mean that prices and reimbursement conditions are the same for all countries as the final decisions will ultimately be taken nationally. This is very different from a joint EU HTA procedure. The joint clinical assessment should be used by all the member states, but the economic assessment and appraisal takes place in the individual member state.

The results of the study show that joint decision rules according to assessment and appraisal among BeNeLuxAI countries would be more promising than its detailed unification of the national HTA methods.

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