Improving patient access to gene and cell therapies for rare diseases in Europe

A review of the challenges proposals for improving patient access to advanced therapeutic medicinal products in the Netherlands

V1

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Chaired by:

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Reader notes:

This document contains country-specific insights on challenges and potential solutions to patient access to advanced therapeutic medicinal products (ATMPs) for patients with rare diseases.

The purpose of the document is to provide a starting point for country-specific engagement and discussion within multi-stakeholder meetings.

The challenges and solutions were discussed and prioritised with members of the RARE IMPACT Working Group in meetings and WebEx's between September 2018 and September 2019. Country-specific challenges/solutions have drawn on global recommendations previously published by EUCOPE and ARM, both members of the Working Group.

The challenges and solutions contained within this document are those that have been proposed as priorities for discussion with local stakeholders by members of the Working Group – the report does not include all challenges identified during the secondary research or Working Group meetings.

Contents

Executive Summary

The RARE IMPACT initiative was launched at the European Conference on Rare Diseases and Orphan Products in 2018. It is a multi-stakeholder initiative working to improve patient access to gene and cell therapies (or advanced therapy medicinal products [ATMPs])[1]. This patient-focused initiative aims to both assess challenges and propose actionable solutions to concerns regarding patient access to these transformative rare disease treatments in Europe. Through engagement with health technology assessment (HTA) agencies, regulatory bodies, payers, patient groups, clinicians, manufacturers and other experts across Europe, RARE IMPACT partners have proposed ideas to provide better access to ATMPs in Europe.

To date, access to ATMPs has not been straightforward in the Netherlands. Of the first CAR-Ts to launch, one was included in the lock (sluice list) for expensive medicines and not granted automatic reimbursement, and the other was not granted reimbursement for one of its two indications. The next three ATMPs anticipated to launch in 2020 are also likely to be included in the lock. This reflects the scrutiny placed on high-cost orphan medicines in the Netherlands, a theme that was central to the Netherlands' Presidency of The European Council in 2016.

Patient access to ATMPs in the Netherlands is primarily challenged by issues related to the assessment pathway and willingness-to-pay. The Netherlands employs a series of assessment protocols to control expenditure. In theory, hospital (in-patient) medicines, which all ATMPs are likely to be, are immediately eligible for reimbursement at the time of marketing authorisation. However, if the expected cost is high when the medicine is included in the basic package the Minister of Health, Welfare and Sport can first place the product in the lock. These products are subject to a cost effectiveness assessment with an €80K/ICER threshold. Being placed in the lock restricts the reimbursement of medicines until certain criteria are fulfilled and price negotiations are carried out with the Minister of Health, Welfare & Sport, which can take up to 9 months.

The Netherlands Care Institute has acknowledged that the innovation and price of ATMPs "*may have an impact on the way in which these medicines are assessed for admission to the insured package and how they are applied".* Both the lock system and automatic reimbursement pathway pose challenges for ATMPs, but there are amendments that can be made to improve patient access without compromising the existing protocols.

Greater flexibility of evidence acceptability is necessary. ATMPs in rare diseases often have smaller populations, single arm or unblinded studies, and surrogate endpoints that may not be well established. Accepting this data as part of an adaptive assessment process may allow for early patient access while generating additional data. A new process has recently been introduced in the Netherlands that will expand the conditional marketing authorisation of new drugs developed for rare diseases to enable access while compensating for the lack of data provided at launch. This does however require the manufacturer to agree on a reduced price during this period. It is not yet clear how successful this reform will be in facilitating access to ATMPs.

The budget impact threshold that triggers the full lock assessment should be raised for ATMPs. For one-off treatments the budget impact is disproportionately skewed to the early years of introduction, versus treatments that are taken continuously. Managed entry agreements and innovative payment contracts can play a role in managing the budget impact and distributing cost over the duration of benefit. If

[1] Medicines for human use developed from genes, cells or tissues are classified as advanced therapy medicinal products (ATMPs) by the European Medicines Agency (EMA)

ATMPs for rare diseases are to be assessed through the lock process, then the cost effectiveness methodology needs to be adjusted to reflect the specificities of one-off treatments in small populations.

The Netherlands is an active participant in the Beneluxa joint assessment initiative, which was initiated in response to a concern about high-priced medicines. The process seeks to align the methodologies and willingness-to-pay of participating countries. However, no ATMP or orphan-specific assessment processes exist and the same methodological challenges that are observed with the cost-effectiveness assessment in the Netherlands (during lock negotiations) are likely to manifest during joint negotiations. It is not clear that this pathway will facilitate early access to ATMPs.

Guidance is required on the implications for ATMPs within the Beneluxa process. Adjustments to the Beneluxa process for ATMPs should be explored though multi-stakeholder discussions focusing on assessment and cost effectiveness methods, outcomes based contractual agreements with multiple countries that allow for pooling of real-world data, and willingness-to-pay thresholds for ATMPs in rare diseases.

The Netherlands should seek to be a leader in driving cross-border healthcare where regional specialisation of treatment centres can result in higher care standards for patients. The Medicines Evaluation Board (MEB), the agency responsible for issuing marketing authorisation in the Netherlands, has stated that a single treatment centre was "*very vulnerable,…in the event of a failure treatment centre there are no alternative centres*". The MEB recommended the establishment of additional treatment centres but given the complexity of the manufacturing process for many ATMPs, and the requirement for specialisation in ultra-orphan conditions, this is often neither feasible nor desirable. Engagement with European Reference Networks (ERNs) can provide a rationale for the need for single treatment centres and reassure authorities in the Netherlands about access to clinical expertise. It is also possible that within the ERN network 'fall-back' processes could be explored to provide support to any country where a local problem arises. Similarly, assurance should be provided to assessors in the Netherlands on highly regulated manufacturing processes of ATMPs which ensure consistency of quality and supply.

An overview of challenges and proposals for improving patient access to ATMPs in the Netherlands

Domain (Impact)*	Challenge	Potential solution	Feasibility**
Assessment 	**AS1.** Very difficult for ATMPs placed in lock to satisfy ZIN criteria for a positive recommendation	**AS1a.** Reform of the assessment criteria for ATMPs in lock to better reflect evidence constraints **AS1b.** Coverage with evidence generation to reduce uncertainty. Agree registry design with assessors during early scientific advice	++ ++
	AS2. The criteria for inclusion in the lock are problematic for ATMPs	**AS2a.** Raise the lock cost threshold for ATMPs and spread cost over duration of treatment benefit **AS2b.** Early dialogue / horizon scanning to determine likely pathway for assessment of ATMPs	++ ++
Affordability 	**AF1.** Joint procurement via Beneluxa is possible, but variation in approach to assessment and procurement may delay/prevent access	**AF1.** Improve early dialogue with all parties in Beneluxa process to align on assessment approach	+++
	AF2. It is unclear what flexibility exists around ICER thresholds for ATMPs for rare diseases	**AF2.** Flexibility around ICER thresholds needs to be made explicit for ATMPs in rare diseases	++
Availability 	**AV1.** Involvement in joint negotiations may delay access in some situations	**AV1.** Dialogue with Beneluxa stakeholders in order to better prepare for future engagements	++
	AV2. Willingness to use cross-border initiatives is unknown	**AV2.** Increased collaboration on treatment centre optimisation within Beneluxa or other cross-border initiatives	+
Accessibility 	**AC1.** Single treatment centres are not preferred	**AC1.** Engage with treatment centres for coordination with network hospitals (clinical / ERN)	+

Notes: *The working group assessment of the relative impact of the challenge of each domain on patient access is represented by Harvey balls from highest (represented by a full blue Harvey ball) to lowest (represented by an empty, white Harvey ball); **Feasibility: Working Group assessment of feasibility of solutions to be implemented. + low feasibility, ++ medium feasibility, +++ high feasibility.

The collaboration

RARE-IMPACT is a collaboration of three not-for-profit organisations, two trade associations and 18 manufacturers of ATMPs brought together by EURORDIS, a non-governmental patient-driven alliance of patient organisations. The overarching objective of the collaboration is to ensure European patients with rare diseases obtain quick access to gene and cell therapies and to create a sustainable model for manufacturers and payers to maintain patient access and innovation. To achieve this objective, the collaboration has established the following goals:

- Identify challenges that are preventing rare disease patients accessing ATMPs
- Propose actionable solutions to address these challenges
- Utilise these ideas within multi-stakeholder discussions within individual countries and in pan-regional forums

The approach

A framework for categorising barriers to patient access was developed and validated by the collaboration. The framework includes four categories, described in Table 1 below.

Table 1. Framework applied to structuring identified challenges

Category	Description
Assessment (magnitude of benefit)	Challenges related to the assessment of the benefit of ATMPs within pricing and reimbursement processes. This includes topics such as evidence uncertainty, generating comparative data, use of surrogate endpoints and assessment pathways
Affordability (price, cost and funding	Challenges concerning the pricing, funding and affordability of ATMPs, including the application of innovative payment models
Availability (legally available)	Non-regulatory challenges to the product being available within countries, such as those related to cross-border healthcare and hospital exemptions
Accessibility (accessible by patients)	Administrative, service capacity and geographic challenges that delay or prevent patient access to ATMPs

Identification of challenges and proposals for improving patient access

Primary and secondary research was conducted to identify challenges to patient access to ATMPs and potential solutions. Secondary research was conducted to create a database of conceptual and country-specific challenges. This research included:

- A targeted literature search
- Reviewing outputs from other initiatives (e.g., the “Alliance for Regenerative Medicine Recommendations for Timely Access to ATMPs in Europe” and EUCOPE’s “Gene & Cell Therapy – Pioneering Access For Ground-Breaking Treatments”)
- Assessing pathways through which patients access ATMPs in the countries of interest
- Reviewing health technology assessment (HTA) and pricing and reimbursement (P&R) decisions for existing ATMPs

Challenges and potential solutions were supplemented, assessed and prioritised through a review process including:

- Members of the Working Group (including EURORDIS, trade associations, affiliated NGOs, and 18 member companies)
- Country-specific patient associations
- Country level decision makers, such as policymakers, HTA bodies and budget holders
- Experts and advisors, such as healthcare professionals, patient representatives, P&R system experts, ATMP technical experts, economists and academics

In the Netherlands, stakeholders engaged included representatives from:

- The Beneluxa Initiative on Pharmaceutical Policy (an initiative involving health services in Belgium, the Netherlands, Luxembourg, Austria and Ireland)
- VSOP (Association of Cooperating Parent and Patient Organizations), the umbrella organization for rare and genetic disorders in the Netherlands

Following stakeholder engagement, the challenges and solutions were refined and prioritised to reflect the perceived importance in improving patient access and feasibility of implementation. Therefore, the challenges in this report are not exhaustive of all identified through primary and secondary research but represent the most important issues as determined by stakeholders.

The outputs from this process have been summarised in this report as a basis for discussion within multi-stakeholder meetings in each country and at European level.

ASSESSMENT

Impact: 

Challenge		Proposed solution		Feasibility
AS1.	Very difficult for ATMPs placed in lock to satisfy ZIN criteria for a positive recommendation	**AS1a.**	Reform of the assessment criteria for ATMPs in the lock to better reflect evidence constraints	++
		AS1b.	Coverage with evidence generation to reduce uncertainty. Agree registry design with assessors during early scientific advice	++
AS2.	The criteria for inclusion in the lock are problematic for ATMPs	**AS2a.**	Raise the lock cost threshold for ATMPs and spread cost over duration of treatment benefit	++
		AS2a.	Early dialogue / horizon scanning to determine likely pathway for assessment of ATMPs	++

The Working Group assessment of the **impact** of the challenge relate to all challenges in each domain. The Working Group assessment of **feasibility** relates to the individual or groups of proposed solutions.

Working group identified challenges

Challenge AS1

Very difficult for ATMPs placed in lock to satisfy ZIN criteria for a positive recommendation.

It is likely that all ATMPs will be considered hospital-only products in the Netherlands. In principle, hospital (in patient) medicines are made available automatically in the Netherlands and should be eligible for reimbursement in the basic medical package at the time of market authorisation. There are two routes to access for hospital products:

A. Lock (sluice list): High priority medicines with potentially large budget impact that are subject to a full HTA/CEA assessment with €80K ICER threshold with subsequent price negotiations and potentially conditional reimbursement.
B. Automatic reimbursement: Hospital products not included in the lock go through a relatively short, automatic reimbursement process.

A. The Horizon Scan for Medicines makes an initial assessment of upcoming medicines: which medicines, for which indication, for how many patients, and what is the expected price. In the event of the expected high costs of a medicine when included in the basic package, the Minister of Health, Welfare and Sport may decide to first place the medicine in the lock. This means that the product is only eligible for reimbursement from the basic package if:

- There is a positive package recommendation from Zorginstituut Nederland (ZIN; English translation: The National Health Care Institute);
    - This is done on the basis of the four package criteria: effectiveness, cost-effectiveness, necessity and feasibility
- There are guarantees for proper use;
- The Minister of Health, Welfare and Sport successfully negotiate a price reduction with the manufacturer.

B. With direct reimbursement hospital products not included in the lock go through a relatively short, automatic reimbursement process. If not included in the lock, insurers, doctors, and pharmacists or purchasing groups are responsible for purchasing cost-effectively. This may also result in hospital being required to bare all costs for centre certification for ATMP delivery. Due to the cost, there may be less

willingness to reimburse ATMPs in this scenario as there is less pooling of risk. Without a central assessment and funding route, there may also be an incentive at a local level to use the hospital exemption.

Both routes are difficult for ATMPs. ATMPs are especially likely to be placed in the lock (see Challenge AS2) and be subject to extended negotiations on price before being made available to patients. Of the first CAR-Ts launched, one has been placed in the lock and one has had one indication included in the basic package. The next three ATMPs expected to launch are anticipated to be included in the lock. Route B is unlikely as it is developed for lower cost drugs and would also require local-level negotiation to secure patient access. Such negotiations can be inconsistent, and from the manufacturer's perspective, this creates a challenge due to the time and resources required for each hospital.

There are mechanisms for the granting of conditional reimbursement. During conditional reimbursement, additional data collection is conducted to address data uncertainties. Following the data generation period, a recommendation is made to the Minister of Health, Welfare and Sport to continue the reimbursement or not (based on four domains: necessity, effectiveness, cost-effectiveness and practicability). Continued reimbursement is dependent on meeting conditions such as price agreements and registries. The health ministry recently announced that in June 2020, the conditional financing scheme for rare diseases will be expanded. The policy broadly follows the previous structure and funding but allows for customised research and an extended research period.

Proposed solution AS1a.

Reform of the assessment criteria for ATMPs in the lock to better reflect evidence constraints.

Based on the criteria and experience to date, ATMPs are likely to be placed in the lock (i.e., route A described above). As a result, ATMPs will be required to submit a pharmacoeconomic dossier which includes a cost-effectiveness analysis. The criteria for reimbursement are well established by ZIN;

- Necessity; the severity / burden of disease
- Effectiveness; efficacy of the product according to the principles of evidence-based medicine
- Cost-effectiveness; the relative cost and outcomes compared with an existing treatment
- Feasibility; how sustainable it is to include the product in the benefit package

Generating long-term, comparative data is difficult for ATMPs, creating challenges to satisfy ZIN requirements. Netherlands stakeholders consulted suggested that one-year efficacy data is the minimum required for positive reimbursement and overall survival data is needed for cancer drugs. This is a challenge for ATMPs that are granted conditional marketing authorisation based on Phase 2 trials reflecting the high unmet need they address and their promising data.

As a consequence, in order for patients to receive access to ATMPs, assuming inclusion in the lock, flexibility in the ZIN criteria for assessment of ATMPs is required (e.g., acceptability of single arm trials, surrogate endpoints and small patient populations). Adaption of the GRADE methodology for rating the quality of evidence for ATMPs should be considered if the current assessment procedure is maintained. Alternatively, the use of multi criteria decision analysis (MCDA) methods might provide more flexibility in assessing the benefits of ATMPs.

In some instances, surrogate measures of ATMP effectiveness, such as factor levels in haemophilia, are believed to be indicative of successful treatment and long-term outcomes. Better guidance on the interpretation of surrogate endpoints for ATMPs, such as vector levels and biomarkers, may allow ZIN to make more informed provisional decisions while awaiting additional data. Surrogate measures should be a topic of discussion in early advice, and companies should explore their value as markers alongside

clinical programmes during development. These surrogate measures could be a part of an adaptive assessment process or a conditional reimbursement scheme.

This solution would require reform or reconfiguration of the existing HTA methods and hence require substantial willingness on behalf of assessors to implement. In the most recent publication of products for horizon scanning, ZIN acknowledge that the number of gene therapies will increase and their innovation and price "*may have an impact on the way in which these medicines are assessed for admission to the insured package and how they are applied*". If open consultation is part of reform in the process for ATMPs, proposals could be put forward on:

- Acceptability of surrogate endpoints and biomarkers as part of an adaptive process.
- Technical approaches to extrapolation of long-term benefit.
- Acceptability of indirect treatment comparison (ITC) in the absence of randomised controlled trials (RCTs).
- Incorporating data generated following initial assessment. This would reduce the uncertainty in the clinical effectiveness assessment of the product, with the product being reviewed over time, rather than at a single point in time.

Feasibility: ++
Stakeholders: ZIN, Trade Associations
Timeframe: 6-18 months

Proposed solution AS1b.

Coverage with evidence generation to reduce uncertainty. Agree registry design with assessors during early scientific advice.

Reducing uncertainty around ATMP clinical effectiveness is crucial for securing patient access. ZIN might wish to consider adopting a more adaptive approach to ATMP assessment to help ensure early patient access while requiring additional data to be generated for ongoing re-assessment of the initial decisions.

Registries are central to the development of an adaptive process. The establishment of post-approval registries will help to fill data gaps while allowing early patient access. While marketing authorisation from the EMA often involves a requirement for further data collection, payer agencies can also request continued data collection to inform their decision on the assessment of new therapies. In order to ensure these registries are established at the time of marketing authorisation, their design could be agreed with assessors during early dialogue. The data collected in these registries could be used to confirm clinical trial data and may even lead to improvements in reimbursement if the RWE can show improvements versus standard of care. Parallel consultation with regulators and HTA bodies could help in designing registries that could address concerns about evidence uncertainty. In addition, consultation with relevant patient associations and medical specialists on registry design should be considered.

It is important that RWE is considered, and that the conditional reimbursement procedures that are currently in place can be adapted or even further expanded for ATMPs. To date, the health ministry has shown a willingness to expand its conditional marketing authorisation of new drugs developed for rare diseases, to enable patient access while awaiting mature data generation. For this initiative to be successful, planning for data collection requirements should begin early (ahead of price negotiations) and assessment timelines and endpoints should be reflective of the disease course and the available data on treatment effect. Patients and ATMP clinical experts need to be involved in both the design and the capture of the data.

Feasibility: ++
Stakeholders: ZIN, Ministry of Health, EMA, Trade Associations, Patient Associations, Federation of Medical Specialists
Timeframe: 6-12 months

Challenge AS2.

The criteria for inclusion in the lock are problematic for ATMPs.

There is uncertainty for ATMP manufacturers as to the pathway through which their products will be assessed. The lack of certainty makes planning difficult, increases uncertainty about future revenue, and ultimately reduces the incentives to invest in ATMPs.

Hospital medicinal products can be placed in the lock and are excluded from reimbursement during assessment. As of 1 July 2018, the criteria to place hospital medicines in the lock are laid down in the Healthcare Insurance Decree:

- If the expected cost at the macro level for the treatment of one new indication alone or several new indications together amount to €40m or more per year, all indications are placed in the lock; or
- If the expected costs at macro level for the treatment of a new indication amounts to €10m or more per year and the costs for treatment of the new indication alone amounts to €50,000 or more per patient per year, the indication is placed in the lock.

ATMPs are more likely to meet these criteria than other treatments for rare diseases. This is because ATMP costs are loaded upfront whereas continuously dosed medicines have costs distributed over the duration of therapeutic benefit. Accordingly, both the cost per patient per year and the total budget impact per year are more likely to exceed the defined thresholds, even if the total cost of managing the condition over time is low.

Proposed solution AS2a.

Raise the lock cost threshold for ATMPs and spread cost over duration of treatment benefit.

ATMPs are disproportionately likely to be placed in the lock due to the upfront nature of the cost. Focussing on ATMPs for this reason is unlikely to be economically efficient, as total costs of treatment over five or ten years may in fact be significantly less with a one-off ATMP versus a continuously dosed medicine. It is proposed that the process of prioritising treatments for the lock is revised in one of two ways:

a) Adjust the assessment of cost/budget impact so that it is an average over 10 years, rather than on first year cost alone.
b) Increase the cost/budget impact threshold for ATMPs to allow for the upfront skew of cost.

Feasibility: **++**
Stakeholders: ZIN, Trade Associations
Timeframe: 6-12 months

Proposed solution AS2b.

Early dialogue / horizon scanning to determine likely pathway for assessment of ATMPs.

Correct designation of ATMPs into assessment pathways requires an accurate understanding of the product and the disease population, in particular the likely patient numbers and the future indications. In order to provide the most accurate information to ZIN, and give greater certainty to manufacturers, discussions on assessment pathway should commence early. Ideally this should be a component of early scientific advice or horizon scanning processes. Advanced notice allows manufacturers to prepare and discuss evidence packages for assessment and post-authorisation real-world evidence gathering activities. Patients and clinical experts should also be involved in these discussions. Authorities in the Netherlands have shown an appetite for transparency on their processes which could lead to better dialogue on assessment pathways and criteria.

Feasibility: **++**
Stakeholders: ZIN, Ministry of Health, Trade Associations
Timeframe: 6-12 months

AFFORDABILITY

Impact: 

Challenge		Potential solution		Feasibility
AF1.	Joint procurement via Beneluxa is possible, but variation in approach to assessment and procurement may delay/prevent access	**AF1.**	Multi-stakeholder dialogue to define a Beneluxa assessment and procurement pathway that is suitable for ATMPs	**+++**
AF2.	It is unclear what flexibility exists around ICER thresholds for ATMPs for rare diseases	**AF2.**	Flexibility around ICER thresholds need to be made explicit for ATMPs in rare diseases	**++**

The Working Group assessment of the **impact** of the challenge relate to all challenges in each domain. The Working Group assessment of **feasibility** relates to the individual or groups of proposed solutions.

Working group identified challenges

Challenge AF1.

Joint procurement via Beneluxa is possible, but variation in approach to assessment and procurement may delay/prevent access.

Joint procurement via Beneluxa is a voluntary initiative between member states that may increases the states negotiation power. However, variation in approach to assessment and procurement between participating countries may delay or prevent patient access. This arises if individual country negotiations are required following the lack of agreement during joint negotiation.

While it is a voluntary process, member states may suggest joint negotiations if the proposed drug cost is considered too high to for reimbursement. Under those circumstances, even though it is voluntary for all parties, it might be difficult for manufacturers to object partaking in the negotiation.

The Beneluxa assessment and procurement process seeks to align the methodologies and willingness-to-pay of participating countries. However, no ATMP or orphan-specific assessment processes exist and the same methodological challenges that are observed with the cost-effectiveness assessment in the Netherlands (during lock negotiations) are likely to manifest during joint negotiations. It is not clear that this pathway will facilitate early access to ATMPs.

Proposed solution AF1a.

Multi-stakeholder dialogue to define a Beneluxa assessment and procurement pathway that is suitable for ATMPs

Guidance is required on the implications for ATMPs within the Beneluxa process. Currently, the methods used and the outcomes of previous pilots are likely to make ATMP manufacturers cautious about agreeing to be assessed through Beneluxa. This is unfortunate, as collaboration between member states on ATMP assessment and procurement offers potential advantages for all stakeholders, particularly through the pooling of real-world data and patient experience.

Adjustments to the Beneluxa process for ATMPs should be explored though multi-stakeholder discussions focusing on the following issues:

- How to adjust assessment and cost effectiveness methods to account for inherent evidential uncertainty associated with ATMPs in rare diseases
- How to create contractual agreements with multiple countries that allow for adaptive pricing and the pooling of real-world data
- Willingness to pay thresholds for ATMPs in rare diseases

Multi-stakeholder discussions (including patient representatives) could be part of the early dialogue either directly with ZIN or as part of the Beneluxa process described above on determining the pathway for reimbursement and data requirements. While assessor-manufacturer dialogue as part of horizon scanning with Beneluxa has been articulated, the role of patient representatives is not clear. Patient representatives are consulted within the ZIN process through a patient representative working group, however it is unclear if the patient representatives consulted are disease-area specific or umbrella organisations. According to the Orphan Drug Package Management guidance, patient associations are not included in indication committees that are responsible for advising on the use of orphan drugs for individual patients. In general, there is a need to raise public awareness via patient organisations and general advocacy in the political and public sphere.

This is aligned with the EUCOPE recommendation for collaboration with all stakeholders to identify approaches to funding, reimbursement and payment mechanisms for appropriate pricing.

Feasibility: **+++**
Stakeholders: ZIN, INAMI, individual companies, Beneluxa coordinators
Timeframe: Immediate

Challenge AF2.

It is unclear what flexibility exists around ICER thresholds for ATMPs for rare diseases

Within the lock assessment process maximum cost effectiveness thresholds are defined as €80K per QALY gained. In practice, there has been some flexibility around this threshold reflecting the specificities of particular treatments and diseases. Such flexibility is aligned with recommendations on the application of cost effectiveness analysis for orphan medicines (such as ORPH-VAL guidelines), which emphasise the need to account for factors such as burden of disease and rarity. However, the extent of this informal flexibility is unclear and may not be sufficient to ensure access to ATMPs in rare diseases, especially given structural challenges inherent in cost effectiveness analysis in one-off treatments in small populations.

Proposed solution AF2.

Flexibility around ICER thresholds need to be made explicit for ATMPs in rare diseases

The ZIN should explore a transparent process whereby ICER thresholds are adapted to reflect the particular circumstances of individual treatment, particularly in rare diseases with high unmet need. Such a reform requires open debate amongst all stakeholders. Manufacturers must be willing to engage in discussions concerning the economics of ATMP development to assuage concerns about the necessity of higher ICERs to ensure continued innovation in ATMPs. Uncertainty around cost effectiveness for individual ATMPs can be addressed through outcomes-based contractual agreements that stagger payments or provide rebates if modelled outcomes are not attained in practice.

Feasibility: ++
Stakeholders: ZIN, individual companies, patient associations, Beneluxa coordinators
Timeframe: Immediate

AVAILABILITY

Impact: 

Challenge		Potential solution		Feasibility
AV1.	Involvement in joint negotiations may delay access in some situations	**AV1.**	Dialogue with Beneluxa stakeholders in order to better prepare for future engagements	**+++**
AV2.	Willingness to use cross-border initiatives is unknown	**AV2.**	Proposal for increased collaboration on treatment centre optimisation within Beneluxa or other cross-border initiatives	**+++**

The Working Group assessment of the **impact** of the challenge relate to all challenges in each domain. The Working Group assessment of **feasibility** relates to the individual or groups of proposed solutions.

Working group identified challenge:

Challenge AV1.

Involvement in joint negotiations may delay access in some situations.

Joint negotiations through the Beneluxa process offer potential advantages for the assessment and procurement of ATMPs in rare diseases. However, currently the process is unlikely to be conducive to fast assessment and reimbursement of these treatments. Other orphan medicines that have been assessed through joint negotiation have had mixed outcomes. In a pilot joint negotiation through Beneluxa, an agreement on the price for a cystic fibrosis treatment was not reached despite two submissions and protracted negotiations on the price. This led to a requirement for further country-level negotiations on the price and a delay of five months after the end of joint negotiations before the treatment became available.

Proposed solution AV1.

Dialogue with Beneluxa stakeholders in order to better prepare for future engagements.

The ethos of the health service in the Netherlands is to ensure patients have access to the best treatments. This core belief means that the health service is open to dialogue and initiating innovative processes, such as Beneluxa, to make treatments available to patients. Dialogue with Beneluxa stakeholders on the unilateral country priorities during horizon scanning could help prepare all stakeholders for efficient negotiations. Additionally, agreeing on the methodology for calculating cost-effectiveness in advance would be beneficial for all parties.

While dialogue is encouraged as part of horizon scanning, the topics for discussion are unknown. In theory, all members have the same objectives, but there is variation in their methodology and willingness to be flexible in order to ensure access. Guidance on how differences in opinions between the country systems on methodology will be resolved to avoid delays in decision making should be provided to avoid breakdowns in the process.

Feasibility: ++
Stakeholders: Beneluxa coordinators
Timeframe: Immediate

Challenge AV2.

Willingness to use cross-border initiatives is unknown

The Netherlands' willingness to use cross-border initiatives is unknown and health services would currently prefer to keep services within their jurisdiction (the MEB's assessment of Strimvelis indicated that a single treatment centre was not favourable). From a European Commission report on the participation of countries in cross-border healthcare collaboration, the Netherlands was judged to be involved in seven projects. However, these projects are not directly linked with the availability of treatments. For example, the Aachen – Maastricht University Hospital collaboration is a health and care workforce training collaboration that allows healthcare professionals to move between hospitals. The Euregio collaboration of parts of Germany, the Netherlands and Belgium enables cross-border emergency care in the Meuse-Rhine region.

Proposed solution AV2.

Increased collaboration on treatment centre optimisation within Beneluxa or other cross-border initiatives

Using existing collaborations as an example, the Netherlands could look to increase collaboration on health services optimisation within Beneluxa or through other forms of cross-border initiatives. Proactive engagement could facilitate alignment on specialist treatment centres, the patient pathway, clinical and manufacturing standards, follow-up and other administrative processes to ensure availability of ATMPs.

The Netherlands are active cross-border collaborators on a number of initiatives in order to improve the availability of healthcare to their citizens. The Netherlands are seen as a driving force within the Beneluxa collaboration and using this position could put forward a proposal for service optimisation for ATMPs if the political will is there to do so.

Feasibility: ++
Stakeholders: ZIN, Beneluxa coordinators, trade associations, ERNs and Patient Associations
Timeframe: Immediate

ACCESSIBILITY

Impact: 

Challenge		Potential solution		Feasibility
AC1.	Variable acceptance of single treatment centres	**AC1.**	Engage with treatment centres for coordination with network hospitals (clinical / ERN)	+

The Working Group assessment of the **impact** of the challenge relate to all challenges in each domain. The Working Group assessment of **feasibility** relates to the individual or groups of proposed solutions

Working group identified challenges

Challenge AC1.

Variable acceptance of single treatment centres

There is variable acceptance of single treatment centres in the Netherlands. They are not preferred by the MEB in the Netherlands due to the risk of a single-point failure. Due to the technical aspects of many ATMPs, most have short shelf lives, and this requires patients to be treated in centres with proximity to the Good Manufacturing Practice (GMP) facilities where these ATMPs are produced. Coupled with a need for clinical expertise in ultra-orphan indications and technical expertise in the manufacturer of ATMPs, often single specialist centres may be more appropriate. However, in their assessment of Strimvelis, the MEB commented that a single treatment centre was "*very vulnerable*" as "*in the event of a failure treatment centre there are no alternative centres*". In order to address this, the MEB recommended the establishment of another treatment centre, but given the complexity of manufacture of many ATMPs, and the variability of approach needed for the different technologies, this is often not feasible.

Proposed solution AC1.

Engage with treatment centres for coordination with network hospitals (clinical / ERN)

European Reference Networks (ERNs) are virtual networks involving healthcare providers across Europe. They aim to tackle complex or rare diseases and conditions that require highly specialised treatment and a concentration of knowledge and resource. Hospitals in the Netherlands are very much part of these networks, for example, Erasmus MC: University Medical Center Rotterdam is part of 18 of the 24 networks.

While not directly addressing the risk of a single-point failure at the treatment centre level, engagement with these ERNs can provide a rationale for the need for single treatment centres and reassure authorities in the Netherlands about access to clinical expertise. It is also possible that within the ERN network 'fall-back' processes could be explored to provide support to any country where a problem arises. While engagement with ERNs may provide assurances over the quality of care in single treatment centres, it will not address the need for single treatment centres in certain scenarios.

Feasibility: +
Stakeholders: ERNs, specialist treatment centres
Timeframe: Immediate

Bibliography

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Appendix

Country profile:

Market type	Cost utility analysis
Position in launch sequence	Early
Previous experience with ATMPs	Unknown

	Status	Note
Strimvelis	Not assessed by ZIN	
Holoclar	Not assessed by ZIN	
Zalmoxis	Not assessed by ZIN	
Glybera	Not assessed by ZIN	
Imlygic	Not assessed by ZIN	
Provenge	Not assessed by ZIN	
MACI	Not assessed by ZIN	
ChondroCelect	Not assessed by ZIN	
Yescarta	In the lock for expensive hospital medicines[1]	Will enter the basic package on basis of outcome of price negotiation[1]
Kymriah	ZIN recommends ALL inclusion for basic package[2] ZIN does not recommend DLBCL for basic package[3]	ALL: Eligible conclusion basic package based on compliance with established medical requirements and would have limited budget impact.[2] DLBCL: Not recommended as it did not fulfil statutory criterion. New data indicating cost-effectiveness could enable future recommendation.[3]
Alofisel	Not assessed by ZIN	
Luxturna	In the lock for expensive hospital medicines[4]	Will enter basic package based on positive recommendation, guarantee for appropriate use and the outcomes of price negotiation[4]
Zolgensma	Shortlisted for placement in the lock – 2019[5]	
Zynteglo	In the lock for expensive hospital medicines – 2019[5]	

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