HICT

Cross-border healthcare for ATMPs

A BELGIAN CROSS-STAKEHOLDER PERSPECTIVE

OPTIMISING HEALTHCARE

This report covers insights from a roundtable discussion in Belgium, held on 13 September 2022 in Brussels.

This roundtable discussion was organized by Hict with input from a group of companies specialized in the development of treatments for rare diseases (PTC Therapeutics, Orchard Therapeutics, and Ultragenyx) who have promoted/ joined the project and supported it financially and/or logistically. This document does not focus on specific diseases or treatments including, but not limited to, those commercialized or experimented by the supporting companies.

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Abbreviations

ATMP	Advanced Therapy Medicinal Products
CM	*Christelijke Mutualiteit*
CBHC	Cross-border healthcare
EMA	European Medicines Agency
ERN	European reference networks
HIVA	Research Institute for Work and Society
MEA	Managed entry agreement
RaDiOrg	Rare Diseases Belgium
RIZIV/INAMI	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering/ Institut National d'Assurance Maladie Invalidité
SPOC	Single point of contact
SSF	Special Solidary Fund
UZA	*Universitair Ziekenhuis Antwerpen*

Introduction

Context

Advanced therapy medicinal products (ATMPs) are medicines for human use based on genes, tissues, or cells, offering transformative new treatment opportunities[1]. They represent an emerging and rapidly evolving market[2]. Their use commonly requires highly specialized clinical expertise and infrastructure and often targets small patient populations (i.e. (ultra-)rare diseases). Due to the small patient numbers and the complexities related to the delivery of the treatments, treatment centers may not be available in every country. This implies that patients, in order to get access to treatment, have to cross borders.

Cross-border healthcare is "a situation in which the insured person receives healthcare in a Member State other than the Member State of insurance"[3]. A distinction can be made between unplanned cross-border healthcare, planned cross-border healthcare, and healthcare for persons that reside in another country. For cross-border healthcare in the context of treatment with ATMPs for rare diseases, we can restrict our focus to **planned cross-border healthcare**.

In Belgium, a change in law was recently adopted[4] that makes an exception for ATMPs regarding the legal obligations of local availability and continuity for reimbursed products[5]. This exception makes it possible for ATMPs to be reimbursed, while the treatment cannot be provided in a Belgian treatment center. The legislative change demonstrates payer awareness of the specific context of ATMPs and opens the road for planned cross-border delivery of ATMP care. Following this change in national law, the challenges patients encounter to accessing treatment abroad should be assessed, and proposals for overcoming these barriers should be formulated. To initiate this discussion, a multi-stakeholder roundtable was organized in September 2022 in Brussels.

[1] "Advanced therapy medicinal products: Overview". European Medicines Agency (EMA) (https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview)

[2] "Regenerative Medicine in 2021: A Year of Firsts and Records". Alliance for Regenerative Medicine, 2021 (https://alliancerm.org/sector-report/h1-2021-report/)

[3] "Cross-border healthcare in the EU under social security coordination. Reference year 2019". De Wispelaere et al., 2020. (https://ec.europa.eu/social/BlobServlet?docId=23780&langId=en)

[4] Publication in the Belgian official journal (*Belgisch Staatsblad/Moniteur belge*) on 30 May 2022 (https://justitie.belgium.be/nl/belgisch_staatsblad)

[5] *Art.72 bis, KB van 3 juli 1996 tot uitvoering van de wet betreffende de verplichte verzekering voor geneeskundige verzorging en uitkeringen.*

Objective and scope of the roundtable discussion

The **objective** of this multi-stakeholder discussion was to:

(i) Define what cross-border issues currently exist for ATMPs, and

(ii) Identify what practical solutions or guidance can be offered to address these issues within existing regulatory frameworks effectively.

The **scope** of the roundtable discussion was narrowed down to:

ATMPs that have been evaluated and approved for permanent or temporary reimbursement in Belgium, for which cross-border healthcare is required.

The discussion did not cover other important and separate considerations of early (i.e., pre-reimbursement approval) or faster (i.e., through an expedited reimbursement process) access for ATMPs.

The roundtable discussion aimed to be a steppingstone towards tangible, realistic, and pragmatic improvements in how Belgian patients have access to cross-border healthcare for ATMP treatment. This implies that we are focusing on short- to mid-term solutions that can be deployed in a national context. Long-term and supranational solution frameworks should still be kept in mind to ensure that (temporary) national initiatives do not create barriers in the future.

Methods

A broad range of stakeholders and experts were invited to participate in the roundtable discussion. Invitees who responded positively, received a **preread document**, detailing current (European and Belgian) legislation, its possible shortcomings in the context of ATMPs, and suggestions towards possible solutions. The preread was accompanied by a short questionnaire, capturing participants' initial insights and feedback on this topic. These answers were only used to prepare the individual discussions and the roundtable discussion.

Individual preparatory discussions were performed between June and September 2022, either online or face-to-face.

The **roundtable discussion** was held on 13 September 2022 in Brussels, Belgium. The discussion was moderated by prof. Stefaan Callens on behalf of Hict and was held under Chatham House Rules[6].

Participants

In total, we had preparatory discussions with eight different organizations (12 participants), of which six organizations (7 participants) participated to the roundtable discussion.

Table 1. Participants and other attendants

Stakeholders	Organization	Preparatory individual discussion	Participated to the roundtable discussion
Participants			
Government representative	RIZIV/INAMI	✓	✓
Industry representatives	Pharma.be	✓	✓
Patient representatives	RaDiOrg	✓	✓
	Ligue Huntington	✓	✓
Sickness funds	Solidaris	✓	✓
Legal expertise	HIVA	✓	✓
Clinical expertise	UZA	✓	
Other attendants			
Meeting organizers	Hict	✓	✓
Meeting moderator	KU Leuven		✓
Meeting supporters	PTC Therapeutics		✓
	Orchard Therapeutics		✓
	Ultragenyx		

This document has been read and approved by all roundtable participants.

[6] Participants are free to use the information received, but neither the identity nor affiliation of the speaker(s) nor that of any other participant may be revealed.

Results

Premise

> There is a common understanding across all stakeholders that there are still issues to solve within the context of cross-border healthcare for ATMPs. A cross-stakeholder perspective can be of added value to work towards solutions.

Participants agreed that it makes sense to **limit the current discussion to the scope suggested** (i.e., ATMPs that have been evaluated and approved for permanent or temporary reimbursement in Belgium, for which patients will necessarily need to travel abroad to receive treatment).

All participants agree that:

> For patients, in as many ways as possible, the path they follow to get access to treatment should be no different for a product that requires them to cross borders than for a product that does not require them to cross borders.
>
> Access to cross-border healthcare for ATMPs that have been accepted for reimbursement in Belgium should be without delay and not hampered by underlying barriers (e.g., budgetary or payment concerns, or complex approval processes) for any of the stakeholders involved.

It was noted that approval processes linked to payment or financing are an essential step to take, for which time is required to perform this rigorously and correct.

At the start of the meeting, Hict summarized the preread describing the existing cross-border legislation and its possible shortcomings (see Appendix). The preread was found to provide an accurate overview of the current legislation. Several participants did point out that in practice several of the routes included can, and often are, combined when seeking treatment abroad.

Issues and solution building blocks

In the preread to this roundtable, Hict identified key issues in cross-border healthcare for AMTPs. Following the participant interviews, these were grouped into three categories:

1. Issues related to the **authorization process**
2. Issues related to **cost coverage for patients**
3. Issues related to **macro-financial streams**

One participant pointed out there are pre-conditions to be satisfied in order to improve care for rare diseases in general. This requires several actions to be taken, such as a recognition status for rare disease patients, a list of recognized rare diseases, a centralized patient registry for rare diseases. Although this is not within the scope of the roundtable discussion, this should be kept in mind.

For each of these categories of issues, possible solution building blocks were formulated.

1. Authorization process

Issues

Key issues identified during the preparations:

Difficult to identify the most optimal route

Patients as initiator

Lack of support and uniformity in the authorization process

Access to treatment provided by private institutions

During the round table discussion, the first issue discussed was the **patient as initiator**. Patients have the right to initiate and follow-up their authorization request. However, it was argued the problem lies with the full responsibility patients bear for initiating the reimbursement process, without the possibility to share this responsibility with the treating physician.[7] Several problems were mentioned:

- The heterogeneity of patients should be considered: some patients will have no problems to bear this responsibility, while others might lack the skills or consequences to initiate and follow up a request.
- Lack of clear guidelines what an authorization dossier should entail.
- Dependence on the knowledge and support provided by the treating physician or center.
  - As our scope considers cases of (ultra)rare diseases, it is possible that the medical expertise within Belgium is limited to one or only a few clinicians. In some cases, there might be no clinical expert in Belgium with sufficient expertise in the particular (ultra)rare disease.
- If a dossier does not include all the necessary documents, the medical advisor that handles the authorization request can ask for additional information. This then goes via the patient back to the treating physician or treating centers, which can delay the authorization procedure.
  - A participant points out that this regularly happens, even in much more simple dossiers.

Next, **the lack of ATMP-specific expertise of the medical advisor**[8] is also considered an issue by the participants.

- A participant pointed out that patients need to be able to trust the medical advisor has the necessary expertise to make a fair and accurate decision. Another participant argued that, in the context of (ultra)rare diseases, it cannot be expected that the medical advisor has the required expertise for each individual case.
- For reimbursement for an orphan ATMP available in Belgium, a medical advisor can rely on advice from an orphan drug college (see Appendix). In the case of an authorization for cross-border healthcare, this is not automatically foreseen.
- Historically, decentralization of the authorization decisions towards the sickness funds and its medical advisors was preferred to distribute the workload. However, in the context of cross-border healthcare for ATMPs, due to the limited number of approaches, it makes sense to recentralize the decisions to make optimal use of knowledge and experience.
  - It should be clear participants still agreed that regular S2 requests (outside the scope of ATMPs) should still be handled by the medical advisors as they are done today.

[7] For a reimbursed (orphan) ATMP available in Belgium (i.e., outside the scope of cross-border healthcare), the treating specialist can initiate the reimbursement request. See Appendix for background material.

[8] In Belgium, a medical advisor affiliated with the sickness funds is responsible for evaluating the request and making a decision based on the dossier submitted by the patient.

Finally, the authorization process **lacks predictability and transparency**.

- When comparing with authorization for a similar treatment that can be provided in Belgium (see reference situation in the Appendix), there appear to be a different and longer authorization process for cross-border healthcare.
- It was argued that decisions are sometimes influenced by contextual factors. In other words, the lack of clear criteria leaves room for discretionary decisions.
- One participant argued that people directly involved – in particular the patients themselves – receive no feedback about what phase their request is in, when they can expect a decision, or, if denied, for what reasons.
- On the other hand, within the context of ATMPs for (ultra)rare disease, these are – almost by default - very specific situations. This complicates working with predefined criteria.

Possible solution building blocks

The following possible solution building blocks were suggested based on the authorization process for **hadron therapy** (see Appendix for background material on hadron therapy):

- Clear requirements and parameters for the filing of a request. It can be relevant to identify specific Belgian referral centers that can refer patients to the treatment center(s) abroad. This approach allows these centers to build up experience in compiling a comprehensive dossier.
- Authorization decisions to be made by a council or committee, ruling out the dependency on the individual advisor's expertise and experience.

Specific solution building blocks in the context of ATMPs suggested by the participants:

- Assign a **single point of contact (SPOC)** for all the parties concerned, creating transparency and better communication.
- **Centralize the authorization decision** to assure uniformity as well as timely decisions.
  - Given the complexity of the cases, decisions should not be made by an individual, such as a medical advisor alone from a sickness fund.
  - In close cooperation with RIZIV/INAMI, an inter-mutualistic expert (team) could be assigned to support the authorization decisions.
- **Link with international experts**:
  - Because clinical expertise for treatment of (ultra)rare diseases might not be present in Belgium, it should be made possible to include advice obtained from an international expert in the authorization procedure. International experts can be identified via the European reference networks (ERN) or the treatment center abroad.
- **Formal recognition of Belgian referral centers** to assure uniformity of authorization process:
  - Limiting the number of centers that can file requests can increase efficiency.
  - Those centers/specialists involved in diagnosis, are expected to have some knowledge on available ATMP treatment.
  - Recognition of a referral center should be based on predefined criteria, such as the availability of genetic testing or the presence of specific expertise. Ideally, these criteria can ensure a limited number of centers geographically spread over Belgium, creating a balance between centralization and access for patients.
  - A financial compensation can be foreseen for the administrative burden related to these complex dossiers. Compensations could be linked to quality standards.
- **Develop clear criteria** for authorization:
  - Criteria could be developed in cooperation with the centers abroad providing the treatment.
  - People involved should be able to check the status of the authorization request.
  - Agree on strict and transparent timelines.

2. Cost coverage

Issues

Key issues identified during the preparations:

> Coverage of travel- and accommodation costs
>
> Coverage of other medical costs
>
> Some pathways require upfront payment

Cross-border healthcare in the context of ATMPs is not limited to the drug costs and administration of the product itself. Other costs or medical care, as mentioned by the participants:

- Specialized interventions that are required to administer the product (e.g., surgical interventions).
- Pre-care and aftercare: patients might need additional testing that can only be done in the guest country, follow-up of adverse events that ask for specific expertise, etc.
- Travel- and accommodation costs: for the patient itself as well as for a possible accompanying parent (or another informal caregiver).

Currently, the patient can request financial support from the Special Solidarity Fund (SSF'), albeit in a separate request. Issues that were mentioned related to this current practice:

- Financial support from the SSF must be requested before travelling abroad. If patients are not timely informed about this option, they will not be able to benefit from this.
- Separate authorization dossiers can lead to different decisions.

Possible solutions

Following possible solution building blocks were suggested based on the cost coverage for **hadron therapy**:

- When authorization is granted, travel and accommodation should be covered within one joint request. Tariffs and criteria can be aligned with other situations, such as those of the Special Solidarity Fund.
- It might still be required to submit additional requests, e.g., for concomitant treatment. The regular S2-route can be used for this.

Specific solution building blocks in the context of ATMPs suggested by the participants:

- **Definition of the care pathway**, per ATMP:
  - For each ATMP, the process of care should be determined. A generic framework for all ATMPs can be of added value to streamline this process.
  - A distinction should be made between process steps that need to happen abroad (in a specialized center) and process steps that can happen in Belgium. All process steps that can be performed locally should happen in Belgium. This is beneficial for the healthcare budget, patient spendings, and patient wellbeing and comfort.
  - For process steps performed abroad, the care pathway description should include an overview of relevant costs and their payers. This way, differences between countries can be identified and, if needed, tackled upfront.
- For the **care process steps that require patients to seek treatment abroad, all costs** should be covered:
  - This includes cure & care, as well as travel and accommodation.
  - Ideally, this should be covered in one authorization request.
  - Again, clear criteria might be necessary so that unnecessary reimbursement of costs is avoided.

3. Macro-financial streams

Issues

Key-issues identified during the preparations:

> Authorities might need to pay more than agreed on Belgian level, due to differences in tariffs.
>
> ATMPs are likely to enter the market under a managed entry agreement (MEA), which is agreed on a national level.

One participant pointed out that the tariffs that should be adhered to (Belgium or guest country) is determined by the legal route. It was recognized by the group that the Directive route appears to be inoperable (where the tariffs in Belgium would be applicable) in the context of ATMPs, as this route requires full upfront payment by the patient. For ATMPs, the Regulation route (S2-route), where tariffs from the guest country apply, is the only feasible legal backbone (see Appendix for background material on the existing legislative routes).

One participant raised the question why **differences in prices** exist. Although the participants acknowledge that these price differences are not always easily explainable, several reasons are raised why list prices are not uniform across Europe:

- The initial list prices result from national reimbursement procedures, which differ in each country.
- Differential list prices can be justified in light of purchasing power parity (PPP).
- Countries can apply formal price reduction systems over time, which differs between countries. This way, tariffs can change over time, creating possible differences even when the original list price would be identical.
- Taxes on drugs also differ across countries.
- Exchange rates vary over time.

In addition, when countries are bound to pay the price of the guest countries for treatment with high (one-off) costs, countries with lower PPP might not be able to guarantee access to treatments provided in countries with higher PPP.

Possible solutions

Joint initiatives between EU countries can help to **align the tariffs** in Europe. For example, Beneluxa[9] is an initiative aiming to ensure timely access and affordability of medicines across several European countries. This includes cooperating in pricing and reimbursement decisions.

It should be recognized that differences in tariffs cannot be fully avoided. Originally, paying the guest country's tariffs is based on a system of solidarity. The context of ATMPs challenges this principle, making it difficult for individual countries to protect their drug budgets. In the context of ATMPs, all participants agree that it seems reasonable that the Belgian payer should be bound to the Belgian tariff of the drug. To **overcome inevitable differences between tariffs**, an agreement on a 'price-to-pay' mechanism should be established. Two different approaches were suggested by the participants:

- The **drug is ordered in Belgium at the Belgian price**, implying that purchase and payment (by Belgium) can be separated from delivery of the product (at the guest country).
  - Further research is required to assess whether this solution is legally possible within the existing S2 route.

[9] https://beneluxa.org/

- In case the Belgian payer continues to be bound to the tariffs of the guest country, as prescribed by the Regulation, the **manufacturer can provide financial compensation** in response to potential differences in tariffs.
  - A participant suggests that these types of compensations could be arranged within a MEA, that will most likely already be in place for these types of products. Some difficulties are raised based on the current standard practices in MEAs:
    - Financial compensations in MEA are often based on the sales data from that particular country. If the guest country purchases the product, these types of agreement terms should also be added to the MEA of the guest country.
    - MEAs are partly confidential, making it difficult for one country to be involved in agreement terms of other countries.
    - MEAs are, in essence, temporary solutions (to facilitate the *entry* to a market), while financial compensation related to differential tariffs should be continued over time.
    - Some issues related to price differences will be difficult to tackle within a MEA (e.g., price differences arising from differences in VAT).

Minimal requirements for a robust solution

Based on the proposed solution building blocks on the authorization process, cost coverage, and macro-financial streams, a **list of minimal requirements** for a robust solution was proposed by the participating stakeholders:

Assure **uniformity**:
- Decisions of authorization in this context should be centralized
- Receiving authorization should not be dependent on a decision from one individual medical advisor.
- Only a limited number of recognized referral centers should be authorized to file requests.
- Include advice from international experts.
- Develop clear criteria to grant authorization.

Assure **affordability**:
- Only those steps within the entire care pathway that cannot be provided in Belgium should be delivered abroad.
- For those steps within the care pathway that require treatment abroad, medical costs (care & cure) and travel- and accommodation costs should be covered.
- One joint authorization request for all costs creates efficient use of resources.
- A Belgian-specific tariff for the product, agreed upon during the national reimbursement procedure, should be applicable for Belgian patients treated abroad.

Possible solution frameworks

Separate solution building blocks should be brought together, creating a robust and uniform procedure. Based on the individual preparatory discussions, two main solution frameworks were suggested and presented by Hict:

- **Building on top of existing frameworks**, such as the Regulation (S2 route), whether or not supplemented with an agreement on top (e.g., bilateral agreements for cross-border areas) or combined with local frameworks (e.g., the Special Solidarity Fund in Belgium).
- Specific national legislation can be created, **independent from European legislation**, to regulate treatment abroad. This has been done for hadron therapy.

Participants generally agreed it would be challenging to tackle all the existing issues by building on existing frameworks. New national legislation seems to be the most optimal framework to integrate the minimal requirements of a robust solution successfully.

However, the group also expects that the first cases of cross-border healthcare in ATMPs will emerge before new legislation can be put in place. Therefore, a solution built on top of existing frameworks should also be considered.

Ad-hoc framework building on existing legislation

If a solution would be built on top of existing frameworks, it was proposed to **develop a framework consisting of ad-hoc (gentlemen's) agreements or practical guidelines** to streamline S2 requests in the context of ATMP treatment abroad. Elements to be included, as proposed by the participants:

- Informally shift responsibilities of preparing the dossier to the treating physician. The official initiator should remain the patient, as prescribed by the S2 route.
- Next to a request for reimbursement via the S2 route, a simultaneous request at the SSF should always be submitted to cover costs related to travel and accommodation.
- The treatment pathway for each ATMP needs to be clarified upfront so that reimbursement for both the therapy and concomitant treatment can be requested in one joint dossier (via the S2 route).

Possible **advantages** mentioned by the participants:

- Guidelines can be adapted and finetuned without necessarily requiring legislative changes.

Possible **challenges** mentioned by the participants:

- Any ad-hoc framework is bound to the mechanisms tied to the underlying backbone. Examples are:
  - The patient must file the request. If the medical advisor requests more information, the patient will remain a point of contact.
  - Following the S2 route, the feasible backbone, tariffs of the guest countries apply. Solutions for compensating potential differences between tariffs (e.g., agreeing on a 'price-to-pay' mechanism, VAT rates) need to be further explored.
- Many of the minimal requirements for a robust solution are not in line with current legislation. Hence, this framework asks for creative and possibly suboptimal approaches.

A separate agreement: starting from a blank page

If a separate agreement would be developed, it was proposed to establish a **container framework** for all ATMPs and not to develop a framework for each ATMP separately. For each ATMP, a separate decree should be implemented detailing the treatment's specific criteria and care pathway.

Possible **advantages** mentioned by the participants:

- A container framework can prescribe generic requirements while allowing flexibility for each ATMP.
- A different legislative framework can deviate from existing European frameworks, such as the S2 route, making it more feasible to meet all the requirements for a robust solution.

Possible **challenges** mentioned by the participants:

- It will take time to develop a new framework, starting from a blank page, while it is expected that ATMPs requiring cross-border healthcare will be reimbursed soon.
  - When looking at the precedent of hadron therapy, it took approximately five years to have a Royal Decree.
- If legislation needs to be changed, all the necessary changes and requirements must be grouped up front.

Conclusions and potential next steps

All participants agreed that, without any actions taken, it is likely that access will be hampered by several barriers, even for ATMPs that the Belgian payer explicitly accepts. New solutions are required to assure uniformity and affordability of cross-border healthcare for ATMPs. Taken into account current issues related to the authorization process, cost coverage for patients and macro-financial streams, specific minimal requirements were formulated for a robust solution.

Different solution frameworks were explored during the round table discussion, about which participants agreed that a separate framework independent from existing legislation should be developed to meet predefined requirements. This should be a container framework providing a generic structure that should be further tailored to each ATMP. However, in parallel, it might be necessary to foresee short-term temporary solutions that build on top of the Regulation.

Although this round table was a first step in identifying the issues and working towards solutions, further steps will be required to meet the stated premise. More specifically, it should be assessed if both solution frameworks are likely to be feasible and acceptable by all involved stakeholders and who should be involved in further developing the solution frameworks.