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

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

V1

January 2019

Chaired by:

Secretariat support by:

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.

The data on patient access to orphan products points to an association between economic status of a country and the accessibility to orphan products. For example, the public expenditure on orphan drugs as a proportion of all pharmaceutical expenditure in the Czech Republic is 2.25% compared with 3.84% and 6.5% in Austria and Belgium, respectively. The Czech Republic has provided access to CAR-Ts recently, suggesting a willingness to provide access to innovative drugs. But there are challenges related to the assessment of ATMPs, affordability / willingness-to-pay and healthcare service infrastructure to address in order to provide sustainable patient access to these treatments.

There is no clear pathway or exemption in the assessment process for ATMPs in the Czech Republic. Direct negotiations between manufacturers and insurers are required to secure patient access. This requires a cost-effectiveness and budget impact analysis. For highly innovative products, where effectiveness is not well understood at the time of application for reimbursement, conditional reimbursement can be obtained for up to three years. A compassionate use programme (CUP) is also possible in the Czech Republic in advance of launch. Leveraging these two programmes to develop an adaptive assessment pathway would allow mature data to be developed to better inform reimbursement decisions.

With regard to affordability, the Czech Republic use a series of measures to control prices due to a focus on budget impact. Consequently, the introduction of managed entry agreements (MEAs) and innovative funding options should be explored to control expenditure over time. Payers are more likely to find the annuity model of payment less risky if it is contingent on health outcomes being met, which will become evident over time. Hospital budgets will initially be responsible for paying for ATMPs, as health care providers have limited budgets for reimbursement of medicinal products (contracted lump sum from health insurers). A state contribution to the hospital drug procurement budgets for ATMPs could address this.

The Czech Republic is familiar with using bilateral agreements to provide access to healthcare innovation to citizens. This will be of importance for ATMP when few treatments centres will be available across Europe. Czech authorities should proactively prepare for this scenario by establishing protocols for providing timely access.

To date, the Czech Republic has one certified CAR-T treatment centre and as hospitals are technologically advanced, more are in place to become certified centres. However, this will require planning to understand which ATMPs being developed could be provided within the Czech Republic, the typical support services required, and the geographical dispersion. Identifying infrastructure and/or services that can be reconfigured for ATMPs will utilise what is already in place in order to reduce the burden on capital infrastructure. The impact on health service should be addressed as early as possible through horizon scanning to better prepare providers and reduce the time to patient access.

[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)

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

Domain	Challenge		Proposed solution		Feasibility
Assessment 	**AS1.**	No formal HTA for ATMPs identified, and direct negotiations with health insurers requires HTA and budget impact assessments	**AS1.**	Widen the population covered under temporary reimbursement and CUP to generate data to inform an adaptive assessment process	++
Affordability 	**AF1.**	A focus on budget impact does not capture long-term value of ATMPs	**AF1.**	Innovative payment options such as risk-sharing agreements should be explored	+
	AF2.	Hospitals are pressured and incentivised to keep costs low (covered under single health insurer lump sums)	**AF2.**	A state contribution to hospital budgets to support the reimbursement of ATMPs	+
Availability 	**AV1.**	The use of cross-border incentives to get patient access is uncertain	**AV1.**	"Gemeinsam Grenzenlos Gesund" (Unlimited Health Together) cross-border scheme between Czech Republic and Austria could be reconfigured and expanded for ATMPs	++
Accessibility 	**AC1.**	It is unclear if infrastructure required for ATMP delivery is available	**AC1.**	Identify infrastructure/services that can be reconfigured for ATMPs	+

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 gene and cell therapies brought together by EURORDIS, a non-governmental patient driven alliance of patient organisation. The overarching objective for 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 gene and cell therapies (advanced therapeutic medicinal products [ATMPs] as defined in European Union [EU] regulation) at European and country level
- Propose actionable solutions to address these challenges
- Shape change to improve patient access to gene and cell therapies
- Prepare external stakeholders and companies for the access challenges that are likely to be faced with gene and cell therapies
- Educate external stakeholders on gene and cell therapy technology and terminology
- Provide a pre-competitive forum in which manufacturers can share experiences and ideas

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 (does it have 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 (is price appropriate and affordable?)	Challenges concerning the pricing, funding and affordability of ATMPs, including the application of innovative payment models are addressed under affordability
Availability (is it legally available?)	Challenges related to cross-border healthcare and hospital exemptions
Accessibility (can patient access treatment?)	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. Initially, 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., ARM's "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 HTA and 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

Following stakeholder engagement, the challenges were refined to reflect the opinions of the stakeholders and the collaboration. 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.

Once challenges were validated by stakeholders, a list of conceptual solutions was developed through secondary research, internal workshops and further stakeholder engagement. The feasibility of each of the solutions was discussed with the members of the collaboration before being brought to stakeholders for further validation. Following stakeholder engagement, solutions were refined to reflect stakeholder's interpretation of the feasibility of each of the solutions.

ASSESSMENT

Impact: 

Challenge		Proposed solution		Feasibility
AS1.	No formal HTA for ATMPs identified, and direct negotiations with health insurers requires HTA and budget impact assessments	**AS1.**	Widen the population covered under temporary reimbursement and CUP to generate data to inform an adaptive assessment process	++

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 assessment challenges

Challenge AS1.

No formal HTA for ATMPs identified, and direct negotiations with health insurers requires HTA and budget impact assessments.

In the Czech Republic, a formal HTA pathway for ATMPs has not been identified. HTA and budget impact assessments are required for direct negotiations with health insurers. The Czech Republic is one of few countries that have an early access programme allowing patients access before reimbursement has been negotiated. Consequently, a more mature evidence package can be presented by the time reimbursement negotiations take place.

A CUP is also available for ATMPs that have not yet been authorised (only somatic cell therapy or tissue engineering medicinal products). This programme allows access on an individual patient basis, when a specific product can be reimbursed after an application to the payer. This CUP has also been used for the reimbursement of treatments developed under the Hospital Exemption. This is an individual decision and therefore may not be practical for all ATMPs in development.

Proposed solution AS1a.

Widen the population covered under the temporary reimbursement and CUP to generate data to inform an adaptive assessment process.

In the Czech Republic, orphan drugs that are considered highly innovative can be granted temporary reimbursement through the 'highly innovative drug programme' for up to 3 years which enables accelerated patient access. After 3 years timeframe, the innovative products must meet cost-effectiveness and budget impact criteria to get permanent reimbursement. Consequently, the difficulties in assessment remain unless enough data is gathered to satisfy HTA criteria.

Widening the population covered under the CUP would also add to the data package that could be used as part of an adaptive reimbursement process. As the data package matures, more informed decisions can be made, rather than at a single point in time at launch.

To account for evidential uncertainty that may exist at launch, the data collected as part of the CUP and could be part of a risk-sharing programme between insurers and manufacturers. A risk-sharing arrangement amongst a group of insurers, similar to what is seen with CAR-Ts in Germany, could provide a template for ATMPs in the Czech Republic. The pooled risk from the insurers side is matched with an outcomes-based approach from the manufactures who agree a rebate with the insurers should patients not reach prespecified milestones following treatment. Any barriers to annuity payments should also be addressed in order to provide further risk-sharing options to payers. These proposed solutions do not necessarily require entire systematic restructuring.

Feasibility: **++**
Stakeholders: SUKL, CUP coordinators, individual manufacturers
Timeframe: 0–12 months

AFFORDABILITY

Impact: 

Challenge		Proposed solution		Feasibility
AF1.	A focus on budget impact does not capture long-term value of ATMPs	**AF1.**	Innovative payment options such as risk-sharing agreements should be explored	+
AF2.	Hospitals are pressured and incentivised to keep costs low (covered under single health insurer lump sums)	**AF2.**	A state contribution to hospital budgets to support the reimbursement 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 affordability challenges

Challenge AF1.

A focus on budget impact does not capture long-term value of ATMPs.

Budget impact is an area of major focus in the Czech Republic. A focus on budget impact does not capture long-term benefits as it is focused on more short-term view of expenditure. This becomes challenging for ATMPs as they are often associated with large one-off up-front payments when systems are geared towards spreading payment out over the treatment period. Additionally, it means that the health care budget is often regarded in isolation instead of accounting for social care budget savings. Currently, the Czech Republic use a series of measures to control prices due to this focus on budget impact.

Proposed solution AF1.

Innovative payment options such as risk-sharing agreements should be explored.

To solve the challenge of the impact of high up-front costs on budget impact, innovative payment models should be suggested. For the Czech Republic, there is a need to explore risk-sharing agreements and remove any barriers to annuity payments. This would enable the discussion to move away from the short-term budget impact to refocus on cost over a period of time, which is more closely aligned with what the health care system is currently geared to deal with. Payers are more likely to find the annuity model of payment less risky if it is contingent on health outcomes being met, which will become evident over time. This solution additionally would reduce the evidential uncertainty payers are facing with data available at the time of launch.

Feasibility: +
Stakeholders: Health insurers, SUKL, trade association
Timeframe: 0–12 months

Challenge AF2.

Hospitals are pressured and incentivised to keep costs low (covered under single health insurer lump sums).

Hospitals are pressured to keep costs low, as they are covered under single health insurer lump sums. Considering the complexity of these treatments, it is likely to be allocated to few treatment centres. Consequently, the treatment and financial burden of these therapies are likely to be felt by single specialist treatment centres. This creates a risk that hospitals in the Czech Republic will be disincentivised to enable access to ATMPs, as their drug procurement budget will be affected.

Proposed solution AF2.

A state contribution to hospital budgets to support the reimbursement of ATMPs.

To ensure access without widespread reform to the current reimbursement environment, a state contribution to hospital budgets could support the reimbursement of ATMPs and reduce the burden on individual hospital budgets. This will require agreement between hospitals, the state and insurers on the level of funding, criteria to release funding and consistent monitoring. To facilitate and accelerate individual patients' access to treatments, a clear funding mechanism should be established to avoid the possibility of cashflow becoming a barrier to treatment.

Feasibility: +
Stakeholders: SUKL, specialist treatment centres, health insurers
Timeframe: 0–12 months

AVAILABILITY

Impact: 

Challenge		Proposed solution		Feasibility
AV1.	The use of cross-border incentives to get patient access is uncertain	**AV1**.	"Gemeinsam Grenzenlos Gesund" (Unlimited Health Together) cross-border scheme between Czech Republic and Austria could be reconfigured and expanded for 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 availability challenges

Challenge AV1.

The use of cross-border incentives to get patient access is uncertain.

In the Czech Republic, the use of cross-border incentives to get patient access is uncertain. The EU cross-border legislation does not make it a statutory requirement for payers to cover treatment for patients in another EU country if it isn't available in the Czech Republic. This introduces a risk of variation in access to ATMPs for patients. The sustainability of providing coverage future ATMPs that require the use of this cross-border route is uncertain, however some patients were treated in Germany with CAR-T treatments approved and reimbursed by sick funds.

Proposed solution AV1.

"Gemeinsam Grenzenlos Gesund" (Unlimited Health Together) cross-border scheme between Czech Republic and Austria could be reconfigured and expanded for ATMPs.

From a cross-border setting, the "Gemeinsam Grenzenlos Gesund" (Unlimited Health Together) cross-border scheme between the Czech Republic and Austria could be reconfigured to also incorporate ATMPs. The collaboration has pioneered many EU projects over the last 8 years and consists of hospitals in lower Austria and the Czech border regions of South Moravia and South Bohemia. Among others, in 2016 a treaty was sign enabling cross-border emergency health care with regard to cross-border dispatch of ambulances linked through a web application. There are currently additional ongoing projects running over 2019, consequently the current success of the scheme and resources applied suggest a possibility to reconfigure the scheme to also incorporate making ATMPs available.

In addition, as few specialist treatment centres may be used for ATMPs across Europe, Czech authorities should proactively prepare for this scenario by establishing protocols for providing timely access. Manufacturers have a role to play by proactively engaging with health care services on the requirements for cross-border healthcare in terms of manufacturing standards, administration, follow-up and data collection.

Feasibility: ++
Stakeholders: Health insurers, SUKL, trade association, Gemeinsam Grenzenlos Gesund
Timeframe: 0–12 months

ACCESSIBILITY

Impact: 

Challenge		Proposed solution		Feasibility
AC1.	It is unclear if infrastructure required for ATMP delivery is available	**AC1.**	Identify infrastructure/services that can be reconfigured for 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 accessibility challenges

Challenge AC1.

It is unclear if infrastructure required for ATMP delivery is available.

Due to the technical aspects of ATMPs, many 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 manufactured. These centres are required to have intensive care unit capacity and resources for any post-treatment observation and supportive care that may be part of the treatment programme. The readiness of the Czech Republic to adopt novel technologies, or ability to adapt existing infrastructure and care delivery, is not perceived as a likely issue after Yescarta was successfully introduced. In the Czech Republic, the first certified centre was approved at the end of 2019.

Proposed solution AC1.

Identify infrastructure/services that can be reconfigured for ATMPs.

Even though several centres in the Czech Republic are in position to be certified to treat patients with cell therapies, certain planning is required on behalf of health services to identify the impact of availability of ATMPs. This planning requires a thorough understanding of the likely number of ATMPs being developed, the typical support services required, and the geographical dispersion. Identifying infrastructure and/or services that can be reconfigured for ATMPs will utilise what is already in place in order to reduce the burden on capital infrastructure. Undertaking a study to assess these factors, in collaboration with manufacturers, and building on the resulting insights into health service delivery planning process at the national and local levels could ensure ATMP access is routine.

In addition, at the individual ATMP level, considerations of the health service impact of a new treatment should be addressed as early as possible through horizon scanning to better prepare providers and reduce the time to patient access.

Feasibility: +
Stakeholders: SUKL, trade association, individual companies
Timeframe: 0–12 months

Bibliography

The Alliance for Regenerative Medicine. Getting Ready: Recommendations for Timely Access to Advanced Therapy Medicinal Products (ATMPs) in Europe. Available from: http://alliancerm.org/wp-content/uploads/2019/07/ARM-Market-Access-Report-FINAL.pdf. Accessed: June 2019

Balasubramanian G., et al. An overview of Compassionate Use Programs in the European Union member states. *Intractable & Rare disease Research.* 2016 Nov; 5(4): 244–254.

EUCOPE. Gene & Cell Therapy – Pioneering Access For Ground-Breaking Treatments. Available from: https://www.eucope.org/wp-content/uploads/2019/03/eucope_genecell_therapy_november2018.pdf. Accessed: June 2019

Hettle R., Corbett M., Hinde S., et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess*. 2017;21(7):1-204.

Institute for Clinical and Economic Review (ICER) and Office and Health Economics (OHE). Gene Therapy: Understanding the science, assessing the evidence, and paying for value. White Paper. Available from: https://www.ohe.org/publications/gene-therapy-understanding-science-assessing-evidence-and-paying-value.

Kawalec P., et al. Pharmaceutical Regulation in Central and Eastern European Countries: A Current Review. *Front Pharmacol.* 2017; 8: 892. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5741607/

Kefalas P. Cell and gene therapy reimbursement: the CGC approach. 2016. Available from: https://ct.catapult.org.uk/sites/default/files/The-Cell-and-Gene-Therapy-Catapult-approach-to-pricing-and-reimbursement-strategy-development.pdf

Kefalas P. Opportunities and challenges with performance-based pricing schemes for ATMPs. 2017. Available from: https://ct.catapult.org.uk/sites/default/files/publication/P_Kefalas_Performance%20Based%20Schemes_18102017.pdf

Szegedi, M., Zelei, T., Arickx, F. *et al.* The European challenges of funding orphan medicinal products. *Orphanet J Rare Dis.* 2018;13(184)

Touchet N., and Flume M. Early Insights from Commercialization of Gene Therapies in Europe. Genes. 2017. 8:78

WHO. Lower Austria launches a new EU-funded cross-border health care project with South Moravia and South Bohemia. Available from: http://www.euro.who.int/en/health-topics/Health-systems/primary-health-care/news/news/2017/03/lower-austria-launches-a-new-eu-funded-cross-border-health-care-project-with-south-moravia-and-south-bohemia. Accessed 14th of August 2019

Appendix

Country profile

Market type	Budget impact analysis
Position in launch sequence	Late
Previous experience with ATMPs	Unknown

	Status	Note
Strimvelis	No publicly available assessment	
Holoclar	No publicly available assessment	
Zalmoxis	No publicly available assessment	
Glybera	No publicly available assessment	
Imlygic	No publicly available assessment	
Provenge	No publicly available assessment	
MACI	No publicly available assessment	
ChondroCelect	No publicly available assessment	
Yescarta	Available since 28/11/2019[1]	For medical products which are not reimbursed from the national health insurance the price is not regulated and price information is not available via SUKL
Kymriah	Available since 28/11/2019[2]	For medical products which are not reimbursed from the national health insurance the price is not regulated and price information is not available via SUKL
Luxturna	No publicly available assessment	
Alofisel	No publicly available assessment	
Zynteglo	No publicly available assessment	
Zolgensma	No publicly available assessment	

[1]Yescarta. SUKL. Available from: http://www.sukl.eu/modules/medication/detail.php?code=0223073&tab=available
[2]Kymriah. SUKL. Available from: http://www.sukl.eu/modules/medication/detail.php?code=0223073&tab=available