Managing clinical and economic uncertainty in the value assessment of innovative gene and cell therapies – adjustments to health technology assessments and innovative payment models

Callanan, D.1, Sear, R.1, Dziasko, M.1, Hanslik, K.2 1. Dolon, London, United Kingdom. 2. EURORDIS, Brussels, Belgium

1. Introduction

- Gene and cell therapies hold great promise for many patients with rare diseases. Given the potentially curative effect of these treatments for diseases with very high unmet need, regulatory incentives have been put in place to accelerate marketing authorisation (MA) of advanced therapeutic medicinal products (ATMPs). However, a consequence of this acceleration is that at the point of health technology assessment (HTA), the data that are available are often considered immature. This results in considerable uncertainty regarding long-term treatment benefits and challenges for pricing and reimbursement decisions and ultimately, patient access.
- Ways to address this uncertainty include:
- 1. Adjusting HTA processes and decision making criteria to account for the greater uncertainty
- 2. Introducing risk sharing / innovative payment models to manage uncertainty while allowing better patient access.

We assessed countries to understand if either approach has been taken.

2. Objective

- 1. To identify and document any existing and proposed amendments to HTA processes with the explicit intention of supporting the assessment of ATMPs in seven European countries (England, France, Germany, Italy, Netherlands, Spain, Sweden)
- 2. To identify and document the use of innovative payment models agreed for ATMPs that have undergone pricing and reimbursement assessment in seven European countries

3. Methods

A targeted review of the published and grey literature was conducted. Sources include HTA websites, published literature and news websites.

4. Results

- ATMPs have been made available to patients in all countries included in the analysis; however, no formal adjustments to HTA processes specifically for ATMPs have been identified (table 1).
- Innovative payment models for ATMPs have been utilised in six of the countries included in the analysis. These include outcomes-based agreements, payment-by-results and annuity-type payments (see table 2).

5. References

1. Luxturna. NICE. Available from: https://www.nice.org.uk/guidance/hst11/chapter/1-Recommendations 2. Yescarta. NICE. Available from: https://www.nice.org.uk/quidance/qid-ta10214/documents/final-appraisal-determination-document 3. NICE. NICE announces details of health technology evaluation methods review. Available from: https://www.nice.org.uk/news/article/nice-announces-details-of-health-technology-evaluation-methods-review **4**. HAS. Yescarta. Available from: https://www.has-sante.fr/jcms/c_28888882/fr/yescarta-axicabtagene-ciloleucel-car-t-anti-cd19 **5**. G-BA statement on Holoclar. Available from: https://www.g-ba.de/downloads/33-211-140/02-2015_G-BA%20aktuell_April%202015.pdf **6**. Budesverband der Pharmazeutischen Indutrie. 2019. Available from: https://www.bpi.de/de/nachrichten/detail/gsav-bremst-bemuehen-um-patienten-mit-seltenen-erkrankungen 7. Bruce F. Germany to increase data requirements for pricing orphan and other drugs. Pink Sheet. 2019 8. G-BA. public hearing on the draft law for more security in drug supply. Available from: https://www.g-ba.de/downloads/17-98-4779/2019-04-04-PA-AfG-SN-GSAV-G-BA.pdf 9. tamento-di-bambini-con-ada-scid 10. AIFA. Yescarta. Available from: https://www.aifa.gov.it/documents/20142/823882/Comunicato_stampa_AIFA_591.pdf/f041d115-8464-89aa-83af-d01f83d10957 11. AIFA. Kymriah. Available from: https://www.aifa.gov.it/ web/guest/-/aifa-approva-la-rimborsabilita-della-prima-terapia-car-t 12. Zorginstituut. New Horizon Scan Medicines. June 2019 Available from: https://www.horizonscangeneesmiddelen.nl/nieuws/publicatie-juni-2019 13. Riksoverhield. Kamerbrief over beleidskader voorwaardelijke toelating geneesmiddelen. Available from: https://www.rijksoverheid.nl/documenten/kamerstukken/2019/10/22/ kamerbrief-over-beleidskader-voorwaardelijke-toelating-geneesmiddelen. 14. Redaccion Medica. Sanidad estrena nuevo modelo de financiación para fármacos de alto impacto. Available from: https://www.redaccionmedica.com/secciones/industria/sanidad-estrena-nuevo-modelo-financiacion-para-medicamentos-de-alto-impacto-2368 15. Redaccion Medica. Spain, pioneer in CAR-T: approves the financing of Yescarta (Gilead). Available from: https://www.redaccionmedica.com/secciones/industria/espana-pionera-en-cart-aprueba-la-financiacion-de-yescarta-gilead--2967 16. Redaccion Medica. The final commissioning of Valtermed, scheduled for December 2020. Available from: https://www.redaccionmedica.com/secciones/ministerio-sanidad/la-puesta-en-marcha-definitiva-de-valtermed-fijada-para-diciembre-de-2020-5132 **17.** NICE. Imlygic. Available from: https://www.nice.org.uk/guidance/ta410 **18.** NICE. Strimvelis. Available from: https://www.nice.org.uk/guidance/hst7/chapter/4-Consideration-of-the-evidence 19. NICE. Kymriah Available from: https://www.nice.org.uk/guidance/gid-ta10270/documents/final-appraisal-determination-document 20. NICE. Alofisel. Available from: https://www.nice.org.uk/guidance/ta556/evidence/appraisal-consultation-document-committee-papers-pdf-6656697901 21. NICE Holoclar. Available from: https://www.nice.org.uk/guidance/ta467 22. NICE. Spherox. Available from: https://www.nice.org.uk/guidance/ ta508/chapter/3-Committee-discussion 23. HAS. Kymriah. Available from: https://www.has-sante.fr/jcms/c 2891692/fr/kymriah-tisagenlecleucel-car-t-anti-cd19-ldgcb 24. HAS. Luxturna. Available from: https://www.has-sante.fr/jcms/c_2964759/fr/luxturna-voretigene-neparvovec-therapie-genique 25. HAS. Alofisel. Available from: https://www.has-sante.fr/jcms/c_2904636/en/alofisel-darvadstrocel-stem-cell-therapy 26. G-BA. Good reasons for decision. Imlygic. Available from: https://www.g-ba.de/ downloads/40-268-4103/2016-12-15_AM-RL-XII_Talimogen-laherparepvec_D-237_TrG.pdf 27. Jørgensen J et al. (2020) J of Market Access & Health Policy, 8:1 28, G-BA, Luxturna, https://www.g-ba.de/downloads/40-268-6053/2019-10-17 AM-RL-XII Voretigen-Neparvovec_D-436_TrG.pdf 29. G-BA. Alofisel. https://www.g-ba.de/downloads/40-268-5411/2018-11-22_AM-RL-XII_Darvadstrocel D-366 TrG.pdf 30. AIFA. Strimvelis: Available from: https://www.aifa.gov.it/-/strimvelis-autorizzazione-e-rimborsabilita-per-la-terapia-genica-per-il-trattamento-di-bambini-con-ada-scid 31. AIFA. Kymriah. Available from: https://www.aifa.gov.it/web/ quest/-/aifa-approva-la-rimborsabilita-della-prima-terapia-car-t 32. AIFA. Yescarta. Available from: https://www.aifa.gov.it/documents/20142/823882/Comunicato_stampa_AIFA_591.pdf/f041d115-8464-89aa-83af-d01f83d10957 33. AIFA. Alofisel. Available from: https://www.gazzettaufficiale.it/eli/id/2018/10/08/18A06269/SG 34. Gazzetta Ufficiale 2017. Holoclar. Available from: https:// www.gazzettaufficiale.it/eli/id/2017/02/24/17A01287/sg;jsessionid=xLqcmUPBzEB7tT5yWfndhQ__.ntc-as1-guri2b 35. Zorginstituut assessment – Kymriah (ALL). Available from: https://www.zorginstituutnederland.nl/publicaties/adviezen/2018/12/18/pakketadvies-sluisgeneesmiddel-tisagenlecleucel-kymriah-voor-de-behandeling-van-b-cel-acute-lymfatische-leukemie-b-cel-all-bij-kinderen-en-jongvolwassenen-tot-25-jaar 36. ACP advice - Yescarta. Available from: https://www.zorginstituutnederland.nl/publicaties/adviezen/2019/02/01/acp-advies-over-het-sluisgeneesmiddel-axicabtagene-ciloleucel-yescarta 37. Price agreements are needed about Luxturna gene therapy. Available from: https://www.zorginstituutnederland.nl/actueel/nieuws/2020/02/19/prijsafspraken-nodig-over-gentherapie-luxturna 38. Redaccion Medica, Available from: https://www.redaccionmedica.com/secciones/industria/sanidad-financia-alofisel-primera-terapia-celular-alogenica-espanola-3324 39. NT Council assessment Kymriah DLBCL. Available from: https://www.janusinfo.se/download/18.2be42a3a16b7371d07e723cd/1561465190544/Tisagenlekleucel-(Kymriah)-DLBCL-190624.pdf 40. TLV full assessment Kymriah DLBCL. Available from: https://www.tlv.se/download/18.3af515b116b6f4c27dc1db55/1561033968718/ bes190618_underlag_kymriah.pdf 41. NT Council assessment Yescarta. Available from: https://www.janusinfo.se/download/18.2e2250bc16d03ce47629547/1567756961040/Axikabtagenciloceucel-(Yescarta)-190906.pdf 42. TLV full assessment Yescarta. Available from: https://www.tlv.se/download/18.192533fa166f516fb27bb5ab/1542290744988/bes181107_underlag_yescarta.pdf 43. NT Council assessment Luxturna. Available from: https://www.janusinfo.se/download/18.30896a3216dbdf9df5b3d397/1571053054129/ Voretigen-neparvovek-(Luxturna)-191014.pdf 44. TLV full assessment Luxturna. Available from: https://www.tlv.se/download/18.2e325bfb16afd0e62b5285d1/1559141988196/bes190506_underlag_luxturna.pdf

Table 1. HTA assessment processes for ATMPs

COUNTRY	CURRENT ATMP ASSESSMENT PROCESS	POTENTIAL CHANGES IN ATMP ASSESSMENT		
ENGLAND	 ATMPs assessed via the NICE HST (highly specialised technologies) process (e.g., Luxturna)¹ or STA (single technology appraisal) (e.g., Yescarta)² 	 The NICE highly specialised technologies inclusion criteria are under review (published Dec 2020) — no specific amendment for ATMPs anticipated³ 		
FRANCE	 Assessed within existing HAS (high authority for health) process with flexibility afforded to the assessment of evidence for ATMPs⁴ 	 TC (transparency committee) to encourage conditional reimbursement for ATMPs Proposal to make registry a requirement for ATMPs 		
GERMANY	 To date, most ATMPs have been assessed through existing AMNOG process; however, some products have not been assessed as they have been deemed procedures (e.g., Holoclar)⁵ 	 Proposal for the introduction of mandatory data collection for a period of 18 months for orphan products with conditional approval to support price negotiations^{6,7} Proposal for all ATMPs to be considered OMPs and afforded the same exemptions as OMPs (e.g., assumption of benefit automatically granted)⁸ 		
ITALY	 ATMPs undergo the same assessment process as other medicines. To date, 3/5 ATMPs that have successfully completed pricing and reimbursement negotiations in Italy have achieved Innovative status (Strimvelis, Kymriah, Yescarta)⁹⁻¹¹ 			
NETHERLANDS	No special amendments to process for ATMPs. However, the one-off cost of ATMPs means more likely to qualify for inclusion in 'the lock' 12	 ZiN (National health 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"¹² The health ministry recently announced that in June 2020, the conditional financing scheme for rare diseases will be expanded. Continued reimbursement is dependent on meeting conditions such as price agreements and registry enrollment¹³ 		
SPAIN	 National CAR-T plan and expensive medicines plan (centralising decision and funding)^{14, 15} 	 Expansion of use of Valtermed registry system piloted with Yescarta and Kymriah¹⁶ 		
SWEDEN	Assessed within existing process	Extension of conditional reimbursement — further NT council involvement		

Table 2. Identified innovative payment and pricing models for ATMPs

	ENGLAND	FRANCE	GERMANY	ITALY	NETHERLANDS	SPAIN	SWEDEN
Imlygic	Simple Discount ¹⁷		Reimbursed ²⁶				
Strimvelis	Reimbursed at list price following HST ¹⁸			Innovation status PBr agreement ³⁰			
Kymriah	Covered under the Cancer Drugs Fund (coverage with evidence development) & confidential discount ¹⁹	Funding available through <i>liste en sus</i> – evidence collection required for annual reassessment ²³	Outcomes- based agreement (OBA) with rebates based on survival endpoint agreed with VDEK & GWQ ²⁷	Innovation status granted. Payment-by result (Pbr) agreement (3 payments: 1 at infusion, 2. at 6 months, 3. at 12 months) ³¹	Orphan drug arrangement recommended by ZiN (ALL indication only) ³⁵	PBr agreement with payment in 2 instalments linked to patient outcomes (1 at treatment and 1 at 18 months based on achieving complete response) ^{14, 15}	Reimbursed with data collection conditions ^{39, 40}
Yescarta	Covered under the Cancer Drugs Fund (coverage with evidence development) & confidential discount ²	Funding available through liste en sus — evidence collection required for annual reassessment ⁴	OBA with rebates based on survival endpoint agreed with VDEK ²⁷	Innovation status granted. Pbr agreement (3 payments: 1. at 180 days, 2. at 270 days, 3. at 365 days) ³²	Pay-for- performance agreement and restricted reimbursement ³⁶	Pbr agreement with payment in 2 instalments linked to patient survival ^{14, 15}	Reimbursed with data collection conditions ^{41, 42}
Luxturna	Discount within Patient Access Scheme following HST assessment ¹	Funding available through post- ATU setting ²⁴	Reimbursed ²⁸		Pay-for- performance agreement ³⁷		Reimbursed with restrictions ^{43,44}
Alofisel	Not reimbursed ²⁰	Reimbursed with evidence development & reassessment ²⁵	Reimbursed. Price negotiations ongoing ²⁹	Class C not reimbursed ³³		Reimbursed via pay for results model ³⁸	
Holoclar	Discount within Patient Access Scheme ²¹		Not considered a product ⁵	Innovation status granted. PBr agreement ³⁴			
Spherox	Reimbursed ²²						