Managing ATMP Challenges: Focus on European Markets

Payers believe current pricing and reimbursement processes are sufficient to address the challenges presented by ATMPs – but how will these be managed across markets?

Advanced therapy medicinal products (ATMPs) are comprised of gene and somatic cell therapies as well as tissue-engineered products, and promise to reshape therapeutic approaches to a wide range of conditions. ATMPs may be particularly important for severe, untreatable or chronic diseases for which conventional approaches have proven to be inadequate. Current cell and gene therapy research often targets rare hereditary disorders such as severe combined immunodeficiency (SCID), while other developments point to a cure for hemophilia and relief from an incapacitating skin disorder called epidermolysis bullosa.[1]

ATMPs are associated with the expectation of a high price tag, the result of higher costs than for conventional therapies for preclinical development, manufacturing and distribution, especially with regard to ex vivo gene therapies that are highly personalized and require individualized manufacturing.[2] Until now, payers across all markets have had little opportunity to assess ATMPs for pricing and reimbursement; however, more and more of these advanced therapies are on the horizon.

The Evidera Market Access team conducted an investigation in May 2017 with national payers in England, France and Germany to gain insights into the current assessment pathways for ATMP pricing and reimbursement, focusing on the challenges to ATMP market access and potential mitigation strategies to address these challenges.

Existing HTA pathways will still apply

Currently, payers assume that the assessment pathways in place are sufficient and expect little procedural change despite the increasing numbers of ATMPs seeking market access.

Going through available orphan or ultra-orphan pathways where and when needed

If not applicable to the drug or no orphan-specialised route available, regular assessment pathways will be utilised

'The assessment process for ATMPs will be strongly paralleled with that of ultra-orphan drugs, these are recognized by NICE through the HSTE. Both NICE and the SMC are familiar with this process.' Advisor SMC

'Mechanism of action is not truly relevant for the pathway of value assessment – these drugs will face similar pathways as all other drugs.' Working group member G-BA

'Same as for all other drugs – HAS always assess drugs in the same way.' Former member Commission de la Transparence

Though no specific differences in HTA and payer assessment processes are anticipated for ATMPs, it is worth noting that cell-based therapies may be considered as new procedures/treatment methods rather than as drugs. In this case, their assessment for pricing and reimbursement will follow different processes than those associated with conventional drugs.

The Glybera story

The first gene therapy to be commercially approved in the Western world was Glybera (alipogene tiparvovec). Glybera received orphan designation in 2004 and was granted marketing authorization in the European Union in 2012 for the treatment of adults with lipoprotein lipase deficiency (LPLD) who have severe or multiple attacks of pancreatitis despite maintaining a low-fat diet.[3] In 2015, a market price was set for Glybera at €1 million ($1.1 million USD) per treatment.[2]

Glybera's evidence package was based on three interventional clinical studies conducted in the Netherlands and in Canada, in which a total of 27 LPLD patients participated.[3] Primary endpoints included individual median fasting plasma triglycerides, individual median postprandial chylomicrons, and the number of episodes of acute pancreatitis after treatment. Results included a clinically relevant and significant reduction in the frequency of acute pancreatitis.

Payer assessments included

France in 2015: Not reimbursed. Insufficient clinical interest due to a modest, heterogeneous and unsustainable effect on triglyceridemia and the prevention of pancreatitis. Uncertainty over tolerability was also a factor.[4]

Germany: Non-quantifiable additional benefit, time-limited decision to reimburse for registered patients until 31 December 2017.[5]

In the EU, Glybera (2012) and Strimvelis (2016) are the only two approved gene therapies to date, developed by UniQure and GSK, respectively. However, Glybera will not have its marketing authorisation renewed when it expires in October 2017, primarily due to poor market performance.[6]

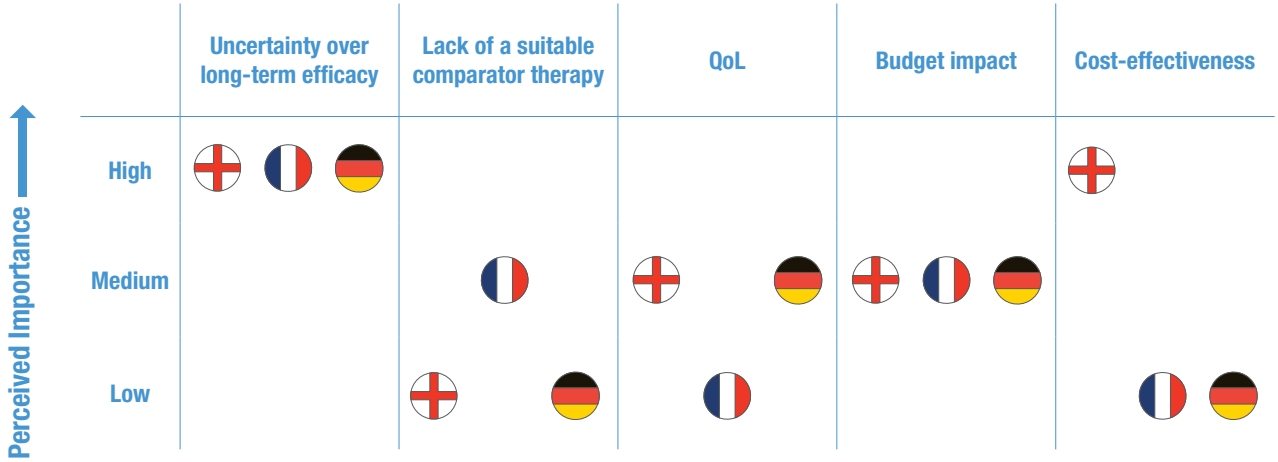
Payers perceive several challenges associated with ATMPs that parallel those for conventional and orphan therapies

Payer responses varied between markets, highlighting the need for manufacturers to tailor reimbursement submissions to specific markets. In general, payers perceived the major challenge to optimal pricing and reimbursement for ATMPs to be uncertainty over long-term efficacy. In England, cost-effectiveness was also deemed to be important in the decision-making process; payers in other markets were far less concerned with cost-effectiveness.

Payers also considered uncertainty over long-term safety to be a major concern but acknowledged that this was more of a regulatory issue and less pertinent to pricing and reimbursement. Overall, payers in the surveyed markets were unconcerned about a lack of suitable comparator therapies for some ATMPs.

Generally, payer perceptions were not markedly different from those related to orphan or traditional therapies. For example, ATMP HTA and payer challenges are much the same as those for new oncology therapies or hypercholesterolemia treatments.

Payer Perception in 2017 of the key challenges to ATMP pricing and reimbursement



So what about management of price and level of access tied to evidence?

The crux for ATMPs is the limited evidence submitted in support of price. This is a common challenge for conventional, orphan, and advanced therapies, but payers anticipate a higher than usual price tag for ATMPs, making the problem particularly pertinent.

Payers were asked to consider a range of innovative schemes and their applicability to ATMPs. Across European markets, indication-based pricing and pricing tied to treatment success were considered attractive options in mitigating the challenges associated with ATMPs.

Hence, for ATMPs the process to price may be a differentiator to conventional therapies rather than the evaluation of value.

> 'The fundamental question is always, can you demonstrate why innovative contracting is better than taking 30% off the list price?' - Member of NICE

	Reimbursement tied to treatment success	Staggered payments*	Indication based pricing**	Other
England	This option addressed the problem of paying for non-responders; however, if the costs of non-responders are weighed in to the price paid for responders then it doesn't make much difference	More beneficial if staggered payments were linked to outcomes	Comes straight out of economics tool box. The challenge to this is whether it can be implemented and policed accurately	Two-part pricing scheme: Fixed-fee to have access to one or more therapies, e.g., something akin to a standing charge or user charge, etc.
France	Could be 'workable' in small populations, but more difficult in larger populations, due to data collection efforts and determination of the appropriate measures	This is a much more attractive option compared to pay for performance	This is difficult to measure	N/A
Germany	Either the evidence exists to support the asking price or it doesn't	Too difficult to implement	Supported by sick-funds and under debate, but implementation may not be over the next 2-3 years, potentially over the next 4-5 years	N/A

* The cost of an expensive therapy would be amortized over time and contingent on proof of the medication's safety and efficacy.

**i.e., one price per indication, independent of whether or not the molecule is an ATMP

Very interesting

Maybe

Not an option

More detailed and holistic considerations of contracting

Innovative contracting and management strategies will be crucial for the commercial success of ATMPs. Preparation for contracting may need to start early in the process and initial assessment should include:

- Which countries can force a contract versus what can be negotiated?
- What are the motivations for manufacturers to propose innovating contracting and management strategies, beyond financial interests?
- What contracting options can be considered?
- Who are the stakeholders at national, regional, and local levels that are involved in initiating, managing, and evaluating contracts?
- What measures are acceptable to demonstrate success?
- Where does the responsibility lie, with manufacturers or payers, to ensure that ATMPs have the best chance to gain market access?

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