MARKET ACCESS TRENDS FOR ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPs) IN EUROPE

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OBJECTIVE

To examine the current EU5 market access landscape for ATMPs

METHODS

Assessed the regulatory path, HTA and reimbursement for ATMPs with European Commission (EC) approval as of September 2018

BACKGROUND

- Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells
- ATMPs can be classified into three main types:
  1. Gene therapy medicines: these contain genes that lead to a therapeutic, prophylactic or diagnostic effect
  2. Somatic-cell therapy medicines: these contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases;
  3. Tissue-engineered medicines: these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue;
- Steady stream of promising clinical results for ATMPs shows progress in the field
- However numerous challenges still exist, in particular, significant R&D investment and market access / commercialization hurdles

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0
https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-017-0818-4 (accessed September 2018)

RESULTS

- EC has approved 12 ATMPs as of September 2018, 8 of which are currently available (Figure 1)
  - 4 ATMPs have been either withdrawn, suspended or marketing authorization hasn't been renewed mainly due to commercial and/or manufacturing reasons (Chondrocelect, Provenge, Maci and Glybera)

Figure 1: EC-approved Cellular & Gene Therapies (ATMPs) on the Market as of September 2018

- HOLOCLAR®: Ex vivo expanded autologous human corneal epithelial cells containing stem cells for treatment of limbal stem-cell deficiency due to ocular burns (EC approval- Feb 17, 2015)
- IMLYGIC™ (talimogene laherparepvec): Talimogene laherparepvec for treatment of adults with unresectable melanoma (EC approval- Dec. 16, 2015)
- Strimvelis: Autologous CD34+ cells transduced to express ADA for treatment of severe combined immunodeficiency due to adenosine deaminase deficiency (EC approval- May 26, 2016)
- ZALMOXIS: Allogeneic T cells genetically modified with a retroviral vector as adjunctive treatment in haploidentical haematopoietic stem cell transplantation (EC approval- Aug 18, 2016)
- spherox: Spheroids of human autologous matrix-associated chondrocytes for repair of symptomatic articular cartilage defects of the knee (EC approval- July 10, 2017)
- ALOFISEL: Darvadstrocel for the treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Chron's disease (EC approval- March 23, 2018)
- YESCARTA® (axicabtagene ciloleucel): Axicabtagene ciloleucel for the treatment of adult patients with diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma (EC approval- Aug 23, 2018)
- KYMRIAH® (tisagenlecleucel): Tisagenlecleucel for the treatment of paediatric and young adult patients up to 25 years of age with B-cell ALL and for the treatment of adult patients with large B-cell lymphoma (EC approval- August 27, 2018)

- Following EC approval, regulatory approval is required at the national level for ATMPs in Germany, Italy and Spain
  - No additional national regulatory authorization is required in France and UK for ATMPs

- Market access status of the 8 available ATMPs varies considerably across the EU5 (Table 1):
  - France: None of the ATMPs are currently reimbursed through normal channels
    - Only one evaluation completed by the HAS, with price negotiations still ongoing
  - Germany: All 8 ATMPs are authorized by the Paul Ehrlich Institute
    - G-BA reviews under AMNOG have been completed for two drugs, one assigned 'no added benefit' (Imlygic) and another 'non-quantifiable added benefit' (Zalmoxis). Of the remaining 6 ATMPS:
      - 2 ATMPs not assessed by the G-BA because they are classified as procedures and not drugs (Holoclar and Spherox)
      - 2 are not marketed in Germany and therefore not listed on Lauer-Taxe or reviewed by the G-BA (Strimvelis, Yescarta)
      - Reviews are ongoing for the remaining two (Alofisel, Kymriah)
    - Reimbursement is available only for the 4 ATMPs listed on the Lauer-Taxe
  - Italy: 4 ATMPs are currently authorized (Holoclar, Imlygic, Strimvelis and Zalmoxis)
    - 3 are reimbursed with financial managed entry agreements and
    - P&R negotiations are ongoing for one ATMP (Imlygic)
  - Spain: While 6 of the 8 ATMPs are currently authorized, none are marketed to date (P&R negotiations are not complete, reimbursement not through standard channels)
  - UK: Final NICE assessments have been published for 4 ATMPs; all of which are recommended for reimbursement (Holoclar, Imlygic, Strimvelis and Spherox)
    - Draft guidelines published for CAR-T cell therapies (Yescarta, Kymriah)
      - Positive assessment only for Kymriah in the pediatric population (included in the reformed Cancer Drug Fund)
      - Adult indications rejected for both therapies based on cost effectiveness
    - SMC has assessed none of the EC-approved ATMPs to date

Table 1: HTA and reimbursement status of ATMPs approved and available in Europe as of September 2018

Brand Name	France	Germany	Italy	Spain	UK (England)^
Holoclar	ASMR IV. Price negotiations not complete	No G-BA review* Reimbursed	Reimbursed. Patient registry; payment-by-results agreement	P&R negotiations not yet concluded	Recommended with restrictions and PAS
Imlygic	Not yet assessed by Transparency Committee	G-BA assessment: No additional benefit. Reimbursed	Class C-nn. Negotiations ongoing		Recommended with restrictions and PAS
Strimvelis		No G-BA review** (not listed in Lauer Taxe)	Reimbursed. Payment-by-results agreement; reimbursed price paid in instalments (confidential)		Recommended as per label
Zalmoxis		G-BA assessment: Non quantifiable additional benefit. Reimbursed (first year free price)	Reimbursed. Patient registry; flat price per patient agreement and safeguard clause (both confidential)		No review to date
Spherox		No G-BA review * (not listed in Lauer Taxe)	P&R negotiations not yet concluded		Recommended with restrictions
Alofisel		G-BA review in development (not listed in Lauer Taxe)	P&R negotiations not yet concluded		NICE review in development
Yescarta		No G-BA review** (not listed in Lauer Taxe)	P&R negotiations not yet concluded		Not recommended in draft guidelines
Kymriah (pediatric)		Review ongoing . Reimbursed (first year free price)	P&R negotiations not yet concluded		Recommended with restrictions –draft?
Kymriah (adult)					Not recommended in draft guidelines

** No G-BA review for Holoclar and Spherox- considered as part of procedure and not as a drug, therefore bypass AMNOG*
***No G-BA review for Strimvelis and Yescarta- Not marketed in Germany*
^ No SMC reviews/decisions published for any of the ATMPs

Reimbursed | Not recommended for reimbursement | Review not published or ongoing- no reimbursement decision made

CONCLUSIONS

- Almost nine years since the first ATMP was approved, market access remains challenging, particularly in France and Spain where none of the ATMPs currently available in Europe are accessible to patients through normal channels
- On the other hand, countries like Germany, Italy and the UK seem to be developing market access pathways primarily based on conditional reimbursement and outcomes/ financial based agreements
- Evolution of payment models and adaptation by countries will continue, as more ATMPs are launched, bringing important health benefits, but also impacting pharmaceutical budgets given the high costs associated with these therapies

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