MARKET ACCESS OF CELLULAR AND GENE THERAPY PRODUCTS IN THE US AND EU5

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OBJECTIVES

- Examine current market access landscape for cellular and gene therapies in the US and EU5 as well as future implications

METHODS

- Assessed market access path for all cellular and gene therapies with FDA and EMA approval as of March 31, 2017
  - 15 cellular therapies approved in the US versus 2 gene therapies and 6 cellular therapies in Europe
- Analyzed HTA assessments and funding mechanisms of these therapies in the EU5

RESULTS

RESULTS (US):

- In the US, cellular and gene therapy products are regulated by the FDA's Center for Biologics Evaluation and Research (CBER) and specifically by the Office of Tissues and Advanced Therapies (OTAT)
  - Classified as therapeutic biological products; a biologic license application (BLA) is required for approval
  - BLA submission process for the first gene therapy to the FDA was initiated in early 2017 (SPK-RPE65 for rare retinal diseases)
- As of 31st March 2017, OTAT has approved 15 cellular therapies for marketing; no gene therapies have been approved thus far (Table 1)
  - First cellular therapy (TheraCys) was approved in May 1990, while latest two (Maci; sterile cord blood collection bags) were approved in December 2016
  - 53.3% (8) of all approved cellular therapies are based on / related to Hematopoietic Progenitor Cells (HPC) from cord blood
  - Manufacturer of TheraCys will be discontinuing its production in mid-2017 because of manufacturing and commercial reasons
- Given the administration of cellular therapies always require supervision, they are covered under medical benefit, although little comprehensive data exists on coverage

RESULTS (EU):

- In Europe, cellular and gene therapy products are assessed by the EMA's Committee for Advanced Therapies (CAT) to confirm whether specific criteria are met by the products to be defined as advanced therapy medicinal products (ATMP)
  - So far, the EMA has approved 8 ATMPs: 2 gene therapies (Glybera; Strimvelis) and 6 cellular therapies
  - Of all approved therapies, five are still marketed (Table 2), while one was suspended and two withdrawn (Table 3)
  - Manufacturer of Glybera will not renew its marketing authorization, expiring end of October 2017, for manufacturing and commercial reasons
  - In comparing cellular and gene therapy products approved by FDA and EMA, only the cell therapy Imlygic is currently marketed in both US and Europe
  - Provenge and Maci are available in the US, but have been withdrawn in Europe because of commercial reasons
- Analysis of HTA assessments and funding mechanisms of these therapies in the EU5 countries (Table 4) showed market access and reimbursement challenges related to uncertain clinical evidence and high costs
  - France: Only two therapies assessed by HAS, of which Glybera benefit was deemed insufficient, while Holoclar was assigned minor improvement in medical benefit (AMSR IV)
  - Germany: Only two therapies assessed by the G-BA, where additional clinical benefit was deemed non-quantifiable (due to orphan drug designation) for Glybera and absent for Imlygic; Holoclar was not considered as a drug but as part of a procedure and was therefore exempted from G-BA assessment
  - Italy: Only two therapies are available and reimbursed- Holoclar and Strimvelis are fully reimbursed as hospital drugs with a payment-by-results agreement; Imlygic is marketed, but currently not reimbursed, in the absence of P&R negotiation
  - Spain: None of the five therapies are currently available
  - UK: Only Imlygic has a NICE assessment and is recommended for restricted use with a patient access scheme; Holoclar and Strimvelis are to be assessed through the NICE HST evaluation process

Table 1. FDA-approved Cellular & Gene Therapies as of March 31, 2017

Brand	Description	FDA approval	Indication / Therapeutic Area
TheraCys	Bacillus Calmette-Guerin (BCG) live intravesical vaccine	May 21, 1990	Treatment and prophylaxis of Carcinoma in Situ (CIS) of the urinary bladder and for the prophylaxis of primary or recurrent stage Ta and/or T1 papillary tumors following transurethral resection (TUR)
Carticel	Autologous Cultured Chondrocytes	Aug 22, 1997	Repair of clinically significant, symptomatic, cartilaginous defects of the femoral condyle
		Mar 2, 2000	Use in patients with inadequate response to a prior arthroscopic / surgical repair procedure
Provenge	sipuleucel-T; Autologous Cellular Immunotherapy	Apr 29, 2010	Treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer
Laviv	azficel-T; Autologous Fibroblasts	Jun 21, 2011	For improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults
Hemacord	HPC Cord Blood	Nov 10, 2011	Unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution
Gintuit	Allogeneic Cultured Keratinocytes and Fibroblasts	Mar 9, 2012	Topical application to surgically created vascular wound bed in the treatment of mucogingival conditions
None yet	HPC Cord Blood	May 24, 2012	Unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution
Ducord	HPC Cord Blood	Oct 4, 2012	Unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution
Allocord	HPC Cord Blood	May 30, 2013	
None yet	HPC Cord Blood (BLA 125432)	Jun 13, 2013	
Imlygic	talimogene laherparepvec	Oct 27, 2015	Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery
None yet	HPC Cord Blood (BLA 125585)	Jan 28, 2016	Unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution
Clevecord	HPC Cord Blood	Sep 1, 2016	
Maci	Autologous Cultured Chondrocytes	Dec 13, 2016	Repair of single or multiple symptomatic, full-thickness cartilage defects of the knee
None yet	Sterile Cord Blood Collection Unit	Dec 21, 2016	Bags for collection of 40 – 250 ml of umbilical cord blood from either vaginal birth or within the sterile field of a cesarean section

Blue cells: therapies based on / related to HPC from cord blood; grey cells: all other therapies

Table 2. EC-approved Cellular & Gene Therapies on the Market as of March 31, 2017

Brand	Generic description	EC approval	Indication
Glybera	Alipogene tiparvovec	October 25, 2012 (exceptional circumstances)	For adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions
Holoclar	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	February 17, 2015 (conditional approval)	Treatment of adult patients with moderate to severe limbal stem-cell deficiency due to ocular burns
Imlygic	talimogene laherparepvec	December 16, 2015	Treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease
Strimvelis	autologous CD34+ cells transduced to express ADA	May 26, 2016	Treatment of ADA-SCID (severe combined immunodeficiency due to adenosine deaminase deficiency)
Zalmoxis	allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	August 18, 2016 (conditional approval)	Adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies

Table 3. EC-approved Cellular & Gene Therapies withdrawn/suspended as of March 31, 2017

Brand	Generic description	EC approval	Indication
Chondrocelect	Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	October 5, 2009 (MA withdrawn on Nov 30, 2016 at the request of the MA holder for commercial reasons)	Repair of single symptomatic cartilage defects of the femoral condyle of the knee (ICRS grade III or IV) in adults
Maci	Matrix-applied characterized autologous cultured chondrocytes	June 26, 2013 (MA suspended since Sep 2014 due to closure of EU manufacturing site)	Repair of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3-20cm2 in skeletally mature adult patients
Provenge	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (sipuleucel-T)	September 6, 2013 (MA withdrawn on May 19, 2015 at the request of the MA holder for commercial reasons)	Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated

Table 4. Market access status of EC-approved Cellular & Gene Therapies as of March 31, 2017

Brand	France	Germany	Italy	Spain	UK-NICE
Glybera	Assessed by Transparency Committee (Nov 2015), but reimbursement not granted because of insufficient medical benefit	Listed in the Lauer-Taxe since November 1, 2014; Hospital use only since October 15, 2015. Non quantifiable additional benefit; temporary AMNOG assessment, set to expire in Jun 2017	Not authorized yet; CTS is still assessing clinical data	Spanish authorization Oct 2014; not yet marketed	Not routinely commissioned- no assessment published
Holoclar	Assessed by Transparency Committee (Jul 2016: ASMR IV; 65% reimbursement), but not yet marketed	Listed in the Lauer-Taxe since Dec 2015; hospital use only; not considered as drug, but as part of a procedure; no AMNOG dossier requested	Hospital only drug; patients registry; payment by results	Spanish authorization Sep 2015; not yet marketed	NICE proposed highly specialized technology evaluation; draft scope (pre-referral) published in March 2016
Imlygic	Not yet assessed by the Transparency Committee	Listed in the Lauer-Taxe since Jun 2016. AMNOG assessment showed no additional clinical benefit	Authorized in Class C-nn (Feb 2017); hospital only drug; AIFA P&R negotiation still ongoing	Spanish authorization Jan 2016; not yet marketed	Recommended by NICE (Sep 2016) with restrictions and Patient Access Scheme
Strimvelis	Not yet assessed by the Transparency Committee	Not yet listed in the Lauer-Taxe. Authorized by the Paul Ehrlich Institut (PEI). Not yet assessed under AMNOG	Hospital only drug; patients registry; AIFA Innovative Status; payment by results; reimbursed price paid in instalments (amount is confidential)	Not authorized yet	NICE proposed highly specialized technology evaluation; draft scope (pre-referral) published in January 2016
Zalmoxis	Not yet assessed by the Transparency Committee	Not yet listed in the Lauer-Taxe. Authorized by the Paul Ehrlich Institut (PEI). Not yet assessed under AMNOG	Not yet assessed by AIFA	Not authorized yet	Not yet assessed by NICE

Source: MME Secondary Analysis of relevant country websites for the EU5

CONCLUSIONS

- It is still "early days" for the evolving market access for cellular and gene therapies in the US and Europe, which seem related to uncertainty with available clinical data and cost issues:
  1. Market access issues experienced to date show the inherent conflict between accelerated regulatory pathways and payers' requirements for solid clinical data
     - FDA has yet to approve a gene therapy, while the two EU approved gene therapies are unlikely to be FDA approved because of clinical trial design issues
     - In Europe, withdrawal/suspension of three ATMPs – with Glybera going to be the fourth – highlights how manufacturing and commercial issues persist even after EMA marketing authorization hurdles have been passed
     - Similarly, in the US, production of cell therapy TheraCys will be stopped in the next months because of manufacturing and commercial reasons
     - FDA's Fast Track designation and EMA's Priority Medicines Program (PRIME) are examples of programs enhancing early dialogue and collaboration between manufacturers and authorities and could potentially help addressing some of these market access issues
  2. However, the commercial experience with cell and gene therapies is limited and immature and should not be taken as directly indicative of how future therapies will be treated
  3. Expected increase in the approved number of cell and gene therapies could benefit all parties, but these expectations will depend on solid clinical evidence and access to these products
     - These therapies, especially if developed as one-time treatments, are usually associated with complex manufacturing process and high costs
     - On the other hand, medical insurances and health authorities are reluctant to reimburse high prices in the absence of clear and long-term clinical data
     - Especially in the US, information on coverage/reimbursement of these therapies is spotty and warrants further investigation
  4. The development of new, cooperative methods to gather and evaluate data for these medicinal products will be needed to unlock their promise in the commercial setting

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