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REAL ACCESS TO ATMPs: THE COST ISSUE

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Introduction

Industry developed and manufactured Advanced Therapy Medicinal Products (ATMPs) which benefit from a centralised marketing authorisation procedure that allows commercialization in all Member States of the European Union (EU), and despite improvement in EU citizen access to ATMPs being stated as one of the two major objectives when the ATMP Regulation was released, actual patient access to ATMPs remains one of the most challenging issues to be addressed.

ATMPs include 4 legal sub-categories : Cell-therapy medicinal products (CTMP), Gene therapy medicinal products (GTMP), Tissue engineered products (TEP) and Combined (Comb.) ATMPs.

Prices of ATMPs are among the highest despite difficulties in proving long term efficacy on significant numbers of patients. Publicly accessible data show prices that vary from several hundreds of thousands euros to several million euros per treatment, with a continuous trend in increasing prices that has fuelled the concept of "financial toxicity" for those and other categories of treatments.

KNOWN PRICES OF THE 26 EU AUTHORISED ATMPs

Commercial Name	Common International Denomination (CID) & Active substance	Type	Domain(s) of application	MA Year	Current status	MA Type	Orph. Med.	Price
ChondroSelect™	Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	TEP	Orthopaedic	2009	Withdrawn 29/07/2016	Standard	✗ N/A	
Glybera™	Alipogene tiparvec	GTMP	Gastrology	2012	Expired 28/10/2017	Exceptional	✓	1,318,432 €*
MACI™	Matrix-applied characterised autologous cultured chondrocytes	Comb. TEP	Orthopaedic	2013	Expired 01/07/2018	Standard	✗ N/A	
Provenge™	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (sipuleucel-T)	CTMP	Oncology	2013	Withdrawn 06/05/2015	Standard	✗	79,953 €*
Holoclar™	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	TEP	Ophthalmology	2015	Ongoing	Conditional	✓	95,000 €** 88,993 €/eye (hidden discount excluded)** 72,288 – 289,151 €* - Lauertaxe at launching: 2,398.50 €** - After negotiation: 1,220.52 €** 1,858 €/vial (hidden discount excluded)**
Imlygic™	Talimogene laherparepvec Modified herpes simplex virus	GTMP	Oncology	2015	Ongoing	Standard	✗	
Strimvelis™	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	GTMP	Immunology (treatment of a specific form of Severe Combine Immune Deficiency or ADA-SCID)	2016	Ongoing	Standard	✓	594,000 €** 594,000 € (+ hospital costs coverage in IT)**
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)	CTMP	Graft vs. host disease in the context of hematopoietic cell transplantation	2016	Withdrawn 09/10/2019	Conditional	✓	189,475 € – 757,899 €* - Lauertaxe at launching: 163,900 €. After negotiation: 130,000 €** 149,000 €**
Spherox™	Spheroids of human autologous matrix-associated chondrocytes	TEP	Orthopaedics	2017	Ongoing	Standard	✗	11,124 € (hidden procurement discount excluded)**
Alofisel™	Darvadstrocel Allogeneic mesenchymal stem cells to treat Crohn's disease fistulae	CTMP	Gastrology	2018	Ongoing	Standard	✓	71,400 €* - 60,000 €** Submitted price: 60,083 €** 54,000 €*** 60,000 €/treatment** 389,130 €* - 327,000 €** 327,000 €, discount**
Yescarta™	Axicabtagene ciloleucel Autologous CAR-T Cells targeting CD19	GTMP	Oncology, haematology (lymphomas various subtypes, acute lymphoblastic leukemias) Now moving in the field of auto-immune diseases	2018	Ongoing	Standard (PRIME)	✓	Confidential price + discount** 327,000 €, recently reduced to 299,000 € + 15,000 € on top of DRG**/** 327,000 €** 275,000 € - 320,000 €** / ***2 320,000 €, discount for DLBC**
Kymriah™	Tisagenlecleucel Autologous CAR-T Cells targeting CD19	GTMP	Oncology, haematology (lymphomas various subtypes, acute lymphoblastic leukemias) Now moving in the field of auto-immune diseases	2018	Ongoing	Standard (PRIME)	✓	313,766 € (hidden discount excluded)** 297,666 € + 15,000 € on top of DRG** 320,000 €** 702,100 €* - 345,000 €** 682,673 € (hidden Discount excluded)** 1,874,250 €* - 1,580,000 € (full price)** / 1,575,000 €***7
Luxturna™	Voretigene neparovec	GTMP	Ophthalmology	2018	Ongoing	Standard	✓	1,6 M€***3 The company left Europe, after failure to reach an agreement with HTA agencies for reimbursement***3
Zynteglo™ in Europe	Betibeglogene autotemcel Autologous CD34+ cells genetically engineered with a lentiviral vector to express a modified version of the human beta-globin gene	GTMP	Haematology (treatment of transfusion-dependent Beta-Thalassemia or TDT and Sickle Cell Disease or SCD with severe vaso-occlusive crises)	2019	Withdrawn 24/03/2022	Conditional/Accelerated (PRIME)	✓	
Zolgensma™	Onasemnogene abeparvovec	GTMP	Muscular Atrophy	2020	Ongoing	Conditional/Accelerated (PRIME)	✓	2,134,550 €*
Libmeldy™	Atidarsagene autotemcel	GTMP	Metabolic diseases (Metachromatic Leukodystrophy)	2020	Ongoing	Accelerated	✓	2,875,000 €***7 2,875,000 £***7
Tecartus™	Brexucabtagene autoleucel Autologous CAR-T Cells targeting CD19	GTMP	Oncology (Lymphoma, Mantle-Cell & Acute Lymphoblastic Leukaemia in adults)	2020	Ongoing	Conditional/Accelerated (PRIME)	✓	360,000 €*
Skysona™	Elivaldogene autotemcel	GTMP	Cerebral adreno leuko-dystrophy	2021	Withdrawn 18/11/2021	Accelerated (PRIME) reverted to Standard	✓	N/A
Abecma™	Idecabtagene vicleucel Autologous CAR-T Cells targeting BCMA	GTMP	Oncology, haematology (multiple myeloma)	2021	Ongoing	Conditional/Accelerated (PRIME)	✓	350,000 €* 419,500 US\$***4
Breyanzi™	Lisocabtagene maraleucel Autologous CAR-T Cells targeting CD19 (balanced composition in CD4+ and CD8+ T-cells)	GTMP	Oncology, haematology (lymphomas various subtypes) Now moving in the field of auto-immune diseases	2022	Ongoing	Accelerated (PRIME)	✗	345,000 €****
Upstaza™	Eladocagene exuparvovec	GTMP	Amino Acid Metabolism, Inborn Errors	2022	Ongoing	Exceptional	✓	4,165,000 €* / 3,500,000 €***7
Carvykti™	Ciltacabtagene autoleucel Autologous CAR-T Cells targeting BCMA	GTMP	Oncology, haematology (multiple myeloma)	2022	Ongoing	Conditional (PRIME)	✓	420,000 €****5
Roctavian™	Valoctocogene roxaparvovec	GTMP	Haemophilia A	2022	Ongoing	Conditional	✓	2,143,960 €*
Ebvallo™	Tabelecleucel Allogeneic T lymphocytes targeting EBV infected cells	CTMP	Post-Transplant Lymphoproliferative Disorders (PTLD) induced by Epstein-Barr Virus (EBV)	2022	Ongoing	Exceptional (PRIME)	✓	N/A
Hemgenix™	Etranacogene dezaparvovec	GTMP	Haemophilia B	2023	Ongoing	Conditional (PRIME)	✓	N/A
Casgevy™	Exagamglogene autotemcel Autologous peripheral blood CD34+ cells genetically engineered through gene edition technology (CRISPR-Cas) to induce expression of foetal hemoglobin	GTMP	Haematology (treatment of transfusion-dependent Beta-Thalassemia or TDT and Sickle Cell Disease or SCD with severe vaso-occlusive crises)	2024	Ongoing	Conditional (PRIME)	✓	1,900,000 €****6

Latest update – May 2024, MA: Marketing Authorisation; OM: Orphan Medicine; DLBC: Diffuse Large B-Cell Lymphoma; DRG: Diagnosis-Related Group

*: Source Antje Behring, Gemeinsame Bundesausschuss (G-BA) German HTA Regulation: Patient access in Germany, Communication ESGCT Congress October 2023 - **: Source Price and reimbursement of advanced therapeutic medicinal products in Europe: are assessment and appraisal diverging from expert recommendations? - ***: Source Dépêches APMnews / ****: APMnews, 09/07/2019 / *****: APMnews, 31/08/2018 / *****: APMnews, 21/10/2021 / *****: APMnews, 25/06/2021 / *****: APMnews, 04/04/2023 / *****: APMnews, 06/02/2024 / *****: APMnews: 18/08/2022 - *****: Source HAS - Avis économique BREYANZI®, 19/12/2023

Challenges

Payment and reimbursement mechanisms as well as decisions on the levels of healthcare expenditures are established at national level and possibly in some countries at regional levels by Healthcare Technology Assessment (HTA) agencies and other governmental bodies, with limited possibilities at the European level.

Mainly apart from the Transparency directive and the recently strengthened collaboration in the field of HTA, adoption of the HTA regulation following the HTA initiatives at the EU level, each Member State is sovereign in determining its health expenses, including to decide on the reimbursement of ATMPs by its National health insurance system.

Actual prices paid by public or private payers are not public, and a significant rebate may result from prior and mutual negotiations between drug manufacturers and healthcare providers, the latter receiving reimbursement from health insurers.

Actual patient access to ATMPs in the European Union is limited and heterogeneous, highlighting the existing gap between the intentions stated in the ATMP Regulation and other EU documents and the actual achievements.

Unsatisfactory situation where patients in need of lifesaving treatments face a shortage on a day-to-day basis, not because of insufficient manufacturing capacities as is the case for low-cost drugs, but because of insufficient payment capacities.

Discussion

The implementation of ATMPs regulation, and a maximal use of non-mandatory procedures under HTA regulation could contribute to enhance coordination in HTA national decisions and fast track patient access to ATMPs.

The development of national procedures to speed up and facilitate access to innovative treatments: in FR, the French national authority for Health (HAS), in collaboration with the French National Agency for Medicines and Health Products Safety (ANSM), grants Early access authorisation for innovative medicines enabling the early availability and funding of a medicinal product before its reimbursement by the National Health insurance system.

Reform of the EU pharmaceutical legislation: The 2023 Proposal for a Directive reforming the Union code relating to medicinal products for human use contains provisions on the responsibility to report on public financial support for the marketing authorisation holder, who "shall declare to the public any direct financial support received from any public authority or publicly funded body, in relation to any activities for the research and development of the medicinal product covered by a national or a centralised marketing authorisation" (Article 57.1).

Foster and promote access to ATMPs at more affordable prices for patients.

Actions taken by the European Commission: The 2024 Communication on Boosting biotechnology and biomanufacturing in the EU identifies actions (streamlining regulatory pathways to help developers navigate the regulatory requirements, establishment of a possible EU Biotech Act, promotion of regulatory sandboxes, fostering public and private investments...) to facilitate and shorten the time and market access for biotech innovations, including ATMPs.

