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The marketing authorisation of Advanced Therapy Medicinal Products under the regulation of the European Union

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BACKGROUND & AIM

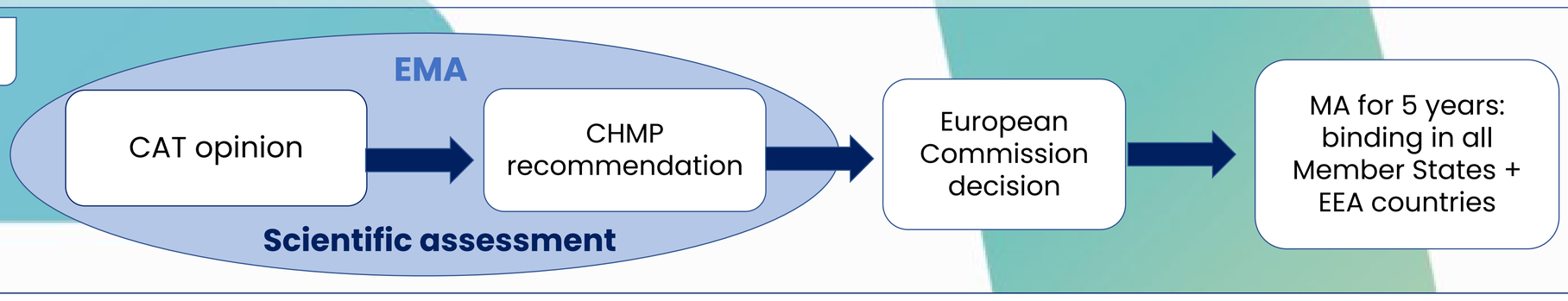
Advanced Therapy Medicinal Products (ATMPs) is a European classification of medicinal products based on genes, cells and tissues specifically regulated in the European Union (EU) from the entry into force of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on ATMPs.

Any company wishing to market ATMPs within the EU must hold a Marketing Authorisation (MA) issued by the European Commission under the "centralised procedure" (CP), after a single application to the European Medicines Agency (EMA) and its scientific assessment involving notably the Committee for Advanced Therapies (CAT). The purpose of the MA is to ensure high quality, safety and efficacy for ATMPs, with a positive risk-benefit balance, to be commercialised.

The CP is the standard procedure to allow MA holders to market ATMPs throughout the EU. The MA shall be refused, suspended or withdrawn if the quality and the safety of the ATMPs is insufficient and if the risk-benefit balance is not favourable. Moreover, expediting MA pathways and regulatory tools have been developed to provide more flexibility and accelerate ATMPs access to the market while other pathways exist for patients to access ATMPs without MA. The latter are alternative to standard CP and possible under strict conditions only.

STANDARD MA

Expensive and time-consuming process which can delay patients' access to ATMPs although provides a wider market access



PROCEDURES AND PROGRAMMES FOR EARLIER ACCESS

EXPEDITING MARKETING AUTHORISATION PATHWAYS

	Accelerated Assessment (AA)	Conditional MA	MA under Exceptional Circumstances
Legal basis	Article 14(9) Reg 726/2004	Article 14a Reg 726/2004	Article 14(8) Reg 726/2004
What	Assessment time for MA ≤ 150 days	Less complete data	Inability to provide comprehensive safety & efficacy data for objective & verifiable reasons
Why	Early access		
How	Major interest for public health (unmet medical needs) Standard MA criteria	Seriously debilitating or life-threatening diseases, emergency situations, orphan drugs, unmet medical needs Standard MA criteria	Rare condition or collection of full information or data is not possible in the state of scientific knowledge or unethical
Who	MA Applicant to European Medicines Agency		
When	Before submission of MA BUT to be discussed earlier via PRIME	Before submission of MA BUT to be discussed earlier via scientific advice / protocol assistance	

SPECIFIC REGULATORY SCHEMES

	Priority Medicines (PRIME)	ATMP PILOT for academia & non-profit organisations
What	An enhanced interaction early dialogue to optimise development plans speed-up evaluation of promising medicines	Enhanced regulatory support for up to five selected ATMPs to optimise their development
Why	To support medicine development	To support translation of basic research into medicine
Criteria	Unmet/high medical need	
How	Fostering early dialogue to improve clinical trials designs	Guiding through the regulatory process
Who	Potential candidate for AA to dedicated person at EMA	Academic/Non-profit ATMP developers to national competent authority or EMA
When	Use of existing routes of approval, especially AA Clinical stages of development (or earlier for academics and SMEs)	Possible to use existing support scheme (e.g., PRIME) Early stages of development (from best practice principles for manufacturing to planning clinical developments)

OTHER PATHWAYS FOR PATIENTS' ACCESS TO ATMPS

	Compassionate use: Groups of patients	Compassionate use: Named-patients basis	ATMP Hospital Exemption
Basis	Article 83 of Regulation 726/2004	Article 5.1 of Directive 2001/83/EC	Article 28.2 of Regulation 1394/2007
What	Under strict condition for seriously ill groups of patients (life-threatening, long-lasting or seriously debilitating illnesses), Undergoing clinical trials or MAA process	For a bona fide unsolicited order, with specifications of an authorised healthcare professional, & for use by an individual patient	ATMP prepared on a non-routine basis, specific quality standards, & used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, to comply with an individual medical prescription
Why	To facilitate & improve access to compassionate use programmes	To fulfil special needs of patients, including without ongoing clinical trials	To enable patients to receive ATMPs under controlled conditions
How	EMA/CHMP recommendations & national rules	National rules	National rules but traceability & pharmacovigilance requirements and quality standards equivalent to ATMPs going through the MA pathway
Who	National competent authority to EMA & Applicant to National competent authority	Applicant to National competent authority	Applicant to National competent authority

The 25 authorised ATMPs in the EU

Name	Type	Domain	MA Year	MA Type	Current status
ChondroCelect	TEP	Orthopaedic	2009	Standard	Withdrawn, 29-07-2016
Glybera	GTMP	Gastrology	2012	Exceptional	Withdrawn, 28-10-2017
MACI	Comb. TEP	Orthopaedic	2013	Standard	Withdrawn, 1-7-2018
Provenge	CTMP	Oncology	2013	Standard	Withdrawn, 6-5-2015
Holoclar	TEP	Ophthalmology	2015	Conditional	Positive
Imlygic	GTMP	Oncology	2015	Standard	Positive
Strimvelis	GTMP	Immunology	2016	Standard	Positive
Zalmoxis	CTMP	Graft vs. host	2016	Conditional	Withdrawn, 9-10-2019
Spherox	TEP	Orthopaedic	2017	Standard	Positive
Alofisel	TEP	Gastrology	2018	Standard	Positive
Yescarta	GTMP	Immunocellular cancer	2018	Standard (PRIME)	Positive
Kymriah	GTMP	Immunocellular cancer	2018	Standard (PRIME)	Positive
Luxturna	GTMP	Ophthalmology	2018	Standard	Positive
Zynteglo	GTMP	Beta-Thalassemia	2019	Conditional/Accelerated (PRIME)	Withdrawn, 24-3-2022
Zolgensma	GTMP	Muscular Atrophy	2020	Conditional/Accelerated (PRIME)	Positive
Libmeldy	GTMP	Leukodystrophy, Metachromatic	2020	Accelerated	Positive
Tecartus	GTMP	Lymphoma, Mantle-Cell	2020	Conditional/Accelerated (PRIME)	Positive
Skysona	GTMP	Cerebral adreno leuko-dystrophy	2021	Accelerated (PRIME) reverted to Standard	Withdrawn, 18-11-2021
Abecma	GTMP	Cancer of plasma cells	2021	Conditional/Accelerated (PRIME)	Positive
Breyanzi	GTMP	Blood cancer	2022	Accelerated (PRIME)	Positive
Upstaza	GTMP	Amino Acid Metabolism, Inborn Errors	2022	Exceptional	Positive
Carvykti	GTMP	Multiple Myeloma cancer of the bone marrow	2022	Conditional (PRIME)	Positive
Roctavian	GTMP	Haemophilia A	2022	Conditional	Positive
Ebvallo	CTMP	Lymphoproliferative Disorders	2022	Exceptional (PRIME)	Positive
Hemgenix	GTMP	Haemophilia B	2023	Conditional (PRIME)	Positive

Latest update - March 2023, TEP: Tissue Engineered Product; GTMP: Gene Therapy Medicinal Product; CTMP: Cell Therapy Medicinal Product; MA: Marketing Authorisation

Results

- Clear increase in approvals from 2018
- Most approved ATMPs are gene therapy medicinal products
- Half of authorised ATMPs benefited from expediting pathways or regulatory support schemes for innovative medicines
- BUT MA withdrawn or not renewed for 7 ATMPs out of 25 authorized ATMPs

CONCLUSION

Even if the EU supports and fosters ATMPs' research, development, and access to market with regulatory tools, patients access to effective and affordable ATMP is limited by the high average cost per patient, the withdrawal of authorised ATMPs from MA holder mostly for commercial reasons, and the differences between healthcare systems and reimbursement strategies of the different Member States.

Although the standard procedure and the expediting MA pathways provide the widest commercialisation of ATMPs in Europe, patients' access to ATMPs is dependent on MA granting and on the MA holder strategy to make the product available in Europe. The latter is linked to the agreement(s) on pricing and reimbursement to provide affordable ATMPs as well as an acceptable financial benefit, including return on investment, for the MA holder.

Patients can also access ATMPs, thanks to other pathways, alternative to MA and possible under strict conditions only. However, depending on how these other pathways can be used according to the applicable national heterogenous rules (e.g., hospital exemption), they could also lead to unfair competition regarding the high requirements for MA granting.