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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

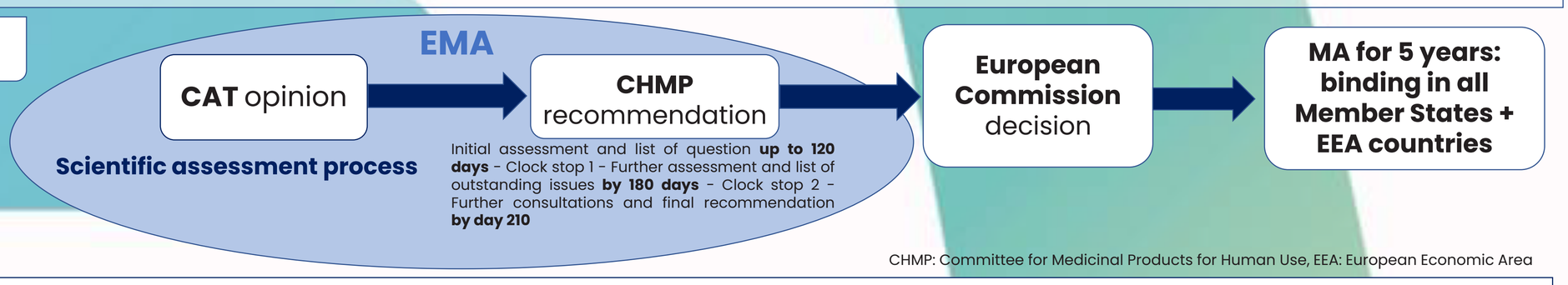
Advanced Therapy Medicinal Products (ATMPs) is a European classification of medicinal products based on genes, cells and tissues specifically regulated in the European Union (EU) from the entry into force of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 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 The MA shall be refused, suspended or withdrawn if the quality and the safety of the ATMPs is insufficient and if the risk-benefit balance is not favourable.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




CHMP: Committee for Medicinal Products for Human Use, EEA: European Economic Area

## PROCEDURES AND PROGRAMMES FOR EARLIER ACCESS

### EXPEDITING MARKETING AUTHORISATION PATHWAYS

| | Accelerated Assessment (AA) | Conditional MA | MA under Exceptional Circumstances |
|---|---|---|---|
| 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

| | 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) |

SME: Small and Medium Enterprises , PRIME: Priority medicines

### 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.