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PRIORITY MEDICINES (PRIME) SCHEME: EVALUATION OF MEDICINES PREVIOUSLY CATEGORIZED IN THE SCHEME AND THEIR CURRENT STATUS

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ABSTRACT

Present review article includes analysis of recently launched PRIME scheme of EMA with the criteria for enrolment. The information related to the benefits that patients and medicine developers can get if they register their drug under this scheme are also discussed. Article also discusses enrolled medicines from the perspective of their therapeutic area/indication, current state of development and authorization status.

KEYWORDS: Advanced therapy medicinal product, Biological preparations, PRIME, Unmet medical need.

INTRODUCTION

The European Medicines Agency (EMA) launches its new PRIME (PRIority MEdicines) scheme on 04 Mar 2016 to strengthen support to medicines that target an unmet medical need. The scheme focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients with no treatment options. These medicines are considered priority medicines within the European Union (EU). Through PRIME, EMA offers early, proactive and enhanced support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicine applications. This will help patients to benefit as early as possible from therapies that may significantly improve their quality of life.[1]

PRIME Eligibility criteria

Products eligible to PRIME support shall[2]

- Target conditions where there is an unmet medical need, i.e. for which there exists no satisfactory method of diagnosis, prevention or treatment in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected;
- Demonstrate the potential to address the unmet medical need for maintaining and improving the health of the community, e.g. by introducing new methods of therapy or improving existing ones.

The available data should support the claim that the product has the potential to bring a major therapeutic advantage to patients in a given indication, through a clinically meaningful improvement of efficacy, such as having an impact on the prevention, onset and duration of the condition, or improving the morbidity or mortality of the disease.

PRIME support features

The following key benefits for applicants are provided:[3]

In early stages of development

- Raising awareness of regulatory requirements early in the development, by providing scientific and regulatory advice on the overall development plan and at major development milestones, with the possibility to involve multiple stakeholders (e.g. Health Technology Assessment (HTA) bodies, patients).
- To help the applicants to overcome financial hurdles to progress through later stages of the development.
- Upon request, micro-, small- and medium-sized-enterprise (SMEs) and applicants from the academic sector may also be eligible for fee reductions on their scientific advice requests, upon case-by-case decisions.

In clinical stages of the development

- Early appointment of Committee for Medicinal Products for Human Use (CHMP) Rapporteur (in line with current process, objective criteria and methodology).
- An initial kick-off meeting with multidisciplinary participation from the EU network, including the CHMP Rapporteur, to discuss the proposed development programme, give preliminary guidance on requirements for marketing authorisation application (MAA), and to develop a schedule for giving regulatory and scientific advice and for

submissions of applications to fulfil legislative requirements (e.g. paediatric investigation plan).
- Scientific advice on key decision points/issues for the preparation of MAA with the possibility to involve multiple stakeholders (e.g. HTA bodies, patients), when relevant. This may also include scientific advice on risk management plan and post-authorisation activities.

Eligible products will also receive coordinated support from EMA throughout the development to address matters related to regulatory aspects.

OBJECTIVE

To evaluate the medicines and their therapeutic area/indication which makes them eligible for the PRIME scheme and their current status of development.

METHODS

The list of medicines, that were granted PRIME eligibility during their development are considered from EMA for the period of Mar 2016 to Dec 2019 and thorough evaluation was carried out to find the parameters that led to the grant and their present status of development.

RESULTS AND DISCUSSION

Upon evaluation, 16 medicines were identified that were granted PRIME eligibility during their development. These are described in Table 1 below.

Table 1: List of medicines evaluated under PRIME scheme from Mar 2016 to Dec 2019.

Preparations	Current Status	Name of the drug	Indication
Advanced therapy medicinal products (ATMP)	2 Withdrawn	Allogeneic umbilical cord blood CD34+ cells cultured ex vivo with Notch ligand Delta1 (NLA101)	Treatment in Haematopoietic Stem Cell Transplantation (HSCT)
		Autologous CD3+ T Cells Expressing CD19 Chimeric Antigen Receptor (JCAR015)	Treatment of relapsed/refractory adult B-cell Acute Lymphoblastic Leukaemia (ALL)
	3 Authorised	Axicabtagene ciloleucel	Treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) who have not responded to their prior therapy, or have had disease progression after autologous stem cell transplant (ASCT)
		Tisagenlecleucel	Treatment of paediatric patients with relapsed or refractory B cell ALL
		Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human βA-T87Q-globin gene (Lentiglobin)	Treatment of transfusion-dependent beta-thalassaemia (also referred to as beta-thalassaemia major)
	1 Under evaluation	Onasemnogene abeparvovec	Treatment of paediatric patients diagnosed with spinal muscular atrophy Type 1
Biological preparations	1 Withdrawn	Aducanumab	Treatment of Alzheimer's disease
	1 Got positive opinion by EMA	Polatuzumab vedotin	Treatment of relapsed and refractory patients with diffuse large B cell lymphoma
	2 Under evaluation	Emapalumab (NI-0501)	Treatment of primary haemophagocytic lymphohistiocytosis (HLH)
		Imlifidase (Recombinant IgG degrading enzyme of Streptococcus pyogenes, HMED-Ides)	Prevention of graft rejection following solid organ transplantation
Chemical preparations	2 Withdrawn	Avacopan (CCX168)	Treatment of patients with active ANCA-associated vasculitis (including granulomatosis with polyangiitis and microscopic polyangiitis)
		Rapastinel	Adjunctive treatment of major depressive disorder
	3 Under	Entrectinib	Treatment of NTRK fusion-positive,

	evaluation		locally advanced or metastatic solid tumours in adult and paediatric patients who have either progressed following prior therapies or who have no acceptable standard therapy
		Bulevirtide	Treatment of chronic hepatitis D infection
		Givosiran	Prevention of acute attacks of hepatic porphyria
Immunological preparation	1 Authorised	Recombinant Vesicular Stomatitis Virus with Envelope Glycoprotein replaced by Zaire ebolavirus (Kikwit Strain) Glycoprotein	Vaccination against Ebola (Zaire strain)

Out of 16 medicines evaluated (presented in Graph 1 below) from Mar 2016 to Dec 2019:

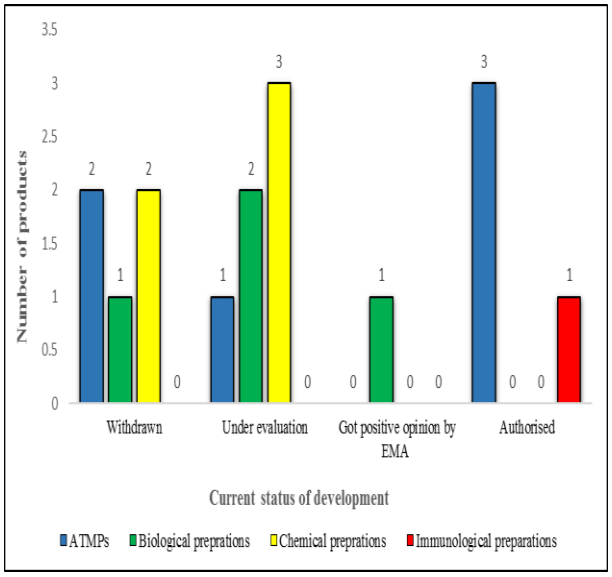
- 5 medicines were withdrawn from this scheme later in their development phase (out of which 2 was for immunology/rheumatology transplantation, 1 was for neurology, 1 was for psychiatry and 1 was oncological preparation), at the request of the applicant. The possible reason for withdrawal of NLA101 and JCAR015 was not available. Further, the application for Aducanumab was withdrawn due to discontinuation of its global Phase 3 trials which indicated that the trials were unlikely to meet their primary endpoint upon completion.[4] Avacopan application was withdrawn by applicant by stating that further data from an ongoing study in over 300 patients receiving treatment for 52 weeks were soon to be available, after which they will submit the full marketing authorisation application.[5] The application for Rapastinel was withdrawn due to results obtained from three pivotal studies that showed rapastinel treatment arms did not differentiate from placebo on the primary and key secondary endpoints. In addition, an interim analysis also suggested the primary and key secondary endpoints will not be met.[6] The summary of reasons for withdrawal is described below in Table 2.

Table 2: List of medicines withdrawn from PRIME scheme.

Name of the drugs	Reason for withdrawal
Allogeneic umbilical cord blood CD34+ cells cultured ex vivo with Notch ligand Delta1 (NLA101)	The reason for withdrawal is unknown, however Nohla therapeutics was granted Orphan Drug designation for this product in HSCT by the European Commission in January 2018.[7]
Autologous CD3+ T Cells Expressing CD19 Chimeric Antigen Receptor (JCAR015)	Development discontinued
Aducanumab	Discontinuation of its global Phase 3 trials which indicated that the trials were unlikely to meet their primary endpoint upon completion
Avacopan (CCX168)	Applicant state that further data from an ongoing study in over 300 patients receiving treatment for 52 weeks were soon to be available, after which they will submit the full marketing authorisation application.
Rapastinel	Results obtained from three pivotal studies showed that rapastinel treatment arms did not differentiate from placebo on the primary and key secondary endpoints. In addition, an interim analysis also suggested the primary and key secondary endpoints will not be met.

- 6 medicines are under evaluation by the CHMP, out of which 1 is oncological preparation, 1 is endocrinology-gynaecology-fertility-metabolism related medicine, 1 is for neurology, 1 is for haematology/hemostaseology, 1 is for immunology/rheumatology transplantation and 1 is a vaccine preparation for infectious diseases, which are described in Table 1 above.
- 1 medicine has got positive opinion by EMA adopted on 14 Nov 2019 (oncological preparation). This medicine was designated as an orphan medicinal product on 16 Apr 2018 and was reviewed under EMA's accelerated assessment programme. This medicine was given PRIME eligibility due to its ability to provide benefit for a rare disorder.
- 4 medicines were authorised to be used in EU. Out of these, 2 are oncological preparations that were granted PRIME eligibility due to their ability to work better against blood cancer which had returned or had stopped responding to previous treatment. Both are advanced therapy medicines called as 'gene therapy product' that works by delivering genes into the body. Both of them were granted orphan designation and are under additional monitoring in EU.[8,9] Another one is for haematology/hemostaseology, which is also an advanced therapy medicine, used to treat a blood

disorder known as beta thalassaemia in patients 12 years and older. This medicine has got conditional marketing authorisation valid throughout the EU and is under additional monitoring.[10] The last one is a vaccine approved for Ebola (Zaire strain) virus. This medicine also got conditional marketing authorisation and is under additional monitoring.[11]



Graph 1: Current status of medicines evaluated under PRIME scheme.

CONCLUSION

Since it is difficult to develop medicines for a small set of patients suffering from a rare disorder or with no treatment option available, EMA launched this scheme to encourage the participation of SMEs or researchers from academic sector to develop medicines in this area by giving them the benefits of PRIME. However, even after its launch from 04 Mar 2016, there are only 4 medicines authorised from PRIME scheme till Dec 2019. The possible reason for which could be the strict selection criteria for drugs under this scheme.

Considering just 3.5 years old launch of this scheme, the actual benefits obtained by the patients in the form of safe and timely access to novel medicines and to companies/medicine developers in the form of accelerated assessments, financial and document assistance, are to be evaluated further in future. At present, this scheme seems to be a good addition to EMA for providing timely access to new therapies in patients with unmet medical need.

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CONFLICT OF INTEREST

There are no conflict of interest.

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