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Early Access Programs (EAPs) in France, Reasons for Refusal

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INTRODUCTION

Patients in France can get access early to drugs that are presumed innovative through so-called Early Access Programs (EAP). A new approval process was established on July 1, 2021 empowering the Haute Autorité de Santé (HAS) to grant EAPs[1]. The HAS is now responsible for early access authorization decisions : the Transparency Commission gives an opinion and the decision is made by the College. These decisions must be issued within short and regulated timeframes, allowing prompt access for patients to medicinal products for indications with an unmet medical need, where those products have also been presumed to be innovative. Authorizations for compassionate use are separate from EAPs and are still within the competency of the French regulatory authority, the Agence nationale de sécurité du médicament et des produits de santé (ANSM).

The reform did not change the key role of the ANSM in establishing the presumption of efficacy and safety of an indication for which a Marketing Authorization (MA) has not been granted. However, the reform gives the HAS the decision-making role in respect of early access authorizations and their public funding coverage. This structure ensures that assessments and decisions are consistent, by creating a continuum of access between derogation-based schemes and the common law funding scheme.

A medicinal product is eligible for an EAP when it is indicated for a severe, rare or incapacitating disease, and when all the following conditions stipulated in article L.5121-12 of the French Public Health Code (CSP) are met[2]:

- There is no appropriate treatment,
- The initiation of the treatment cannot be deferred,
- The efficacy and safety of the medicinal product are strongly presumed based on the results of clinical trials;
- This medicinal product is presumed to be innovative, notably compared with a clinically relevant comparator.

OBJECTIVES

The aim of this research is to list the reasons for refusal of EAP in the first 2 years of the new process, and to identify the main and recurring reasons, and to gather the TC decisions for reimbursement that may have occurred later.

MATERIALS & METHODS

Systematic analysis of the HAS opinions refusing the grant of EAPs between July 1, 2019 and June 30, 2023 cited in the HAS report on this period, and outcomes on their reimbursement (post MA EAP)[3].

RESULTS

Among 164 initial applications for early access authorization, mainly in the field of oncology, 125 dossiers were assessed as of June, 30 2023 and the College issued 27 refusals (21.6%)[3]. Two products were refused more than once (one in 2 indications, one in 3 indications) during the period of the analysis.

Four drugs were refused by ANSM on the basis that efficacy and safety could not be established (among 11 drugs in pre-MA setting) and were not assessed further.

One drug was refused on the basis that it did not treat a rare and serious disease, a basic requirement of EAP.

Most refusals were due to availability of treatment alternatives (17/23, 73.9%) as was the lack of comparative data to establish the added value of the drug candidate (21/23, 91.3%). In these cases, the innovative criteria could not be fulfilled. Interestingly, a drug with an ongoing EAP was considered as an alternative.

Only 4 drugs were presumed innovative and still refused. Here the negative decision was due to the existence of treatment alternatives.

The refusals were mostly based on more than one criterion. The College expressed a different analysis than the Transparency Commission of some of the criteria, mainly in the first dossiers, but changed the TC decision only in 1 case.

Table 1: EAP Dossiers In This Analysis

	n submitted	n submitted	n submitted
pre MA	76	49	11
Oncology			4
post MA	88	76	16
Oncology			10
Total	**164**	**125**	**27**

Table 2: Reasons For Refusal

	Negative Benefit/Risk n=11	Disease not rare/severe n=23	Alternatives exist n=23	Can defer treatment n=23	Not innovative n=23
pre MA	4	1	5	5	5
Oncology	1	1	1	1	1
post MA	NA		12	16	14
Oncology			10	11	9
Total	**4**	**1**	**17**	**21**	**19**

The results of the standard post MA assessment for reimbursement by HAS show that, among the 16 drugs which had obtained a negative decision for post MA EAP[3]:

- 5 were given a medical importance rating (Service Médical Rendu or SMR) “insufficient” in the full population of their label (31%) and thus reimbursement was denied.
- 12 were given an SMR “sufficient”, 7 with an assessment of Amélioration du Service Médical Rendu (ASMR or improvement in medical benefit) rating of ASMR V (‘no added value’) and 4 with an ASMR IV (‘minor added value’).

CONCLUSIONS

Refusals of EAPs by HAS in France are relatively low (21.6 %). The reasons for refusal are widely the same: alternative therapies exist in most cases and comparative data are missing, thus, the added benefit and the “innovative” status cannot be established.

The criteria are very stringent, and manufacturers may be underestimating the existing treatment alternatives and the need for comparative data.

Further TC opinions confirmed these initial assessments, as 31% of these drugs were denied reimbursement, 44% were reimbursed with “no added value” and only 4 of them (25%) were rated as bringing even “minor added value” (ASMR IV).

Pharmaceutical company decision-makers may benefit from this analysis when considering whether to invest time and resources in seeking early access in France, alongside the limited possible commercial returns from most EAPs[4].

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