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Changes to Early Access Scheme in France: Early Learnings for Orphan Drugs

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Background & Objective

Access to orphan drugs (OD) varies considerably across EU countries and is generally slower than for non-orphan.[1] Overall early access (EA) programs provide patients prompt access to promising treatments prior to reimbursement by national authorities and/or their marketing authorization (MA).

In France, the EA programs have been revised and simplified in June 2021.[2] The aim of our analysis was to review the new regulation on EA and assess its impact on ODs access in France.

Methods

New EA regulations and completed EA assessments for OD from July 1st, 2021, until September 21st, 2022, in France were reviewed. The following parameters were of interest: time to access, key criteria considered in EA assessments and subsequent transparency committee (TC) recommendation.

Results

EA regulation in France

With the new regulation, French National Authority for Health (HAS) is now responsible for EA authorization decisions, while the key role of the French National Agency for Medicines (ANSM) remains in establishing the presumption of efficacy and safety in case the drug does not have MA.[2]

The new EA schemes replaced cohort Temporary Authorization for Use – ATUc (pre-MA) and Temporary Funding Scheme – PECT (post-MA). Beyond EA, the new regulation covers compassionate access, however, it was not part of the analysis scope.

Prior to the HAS decision, the TC issues an opinion on fulfilment of eligibility criteria. To be granted EA, the following criteria are considered: 1) Severe, rare or debilitating disease, 2) lack of appropriate treatment, 3) initiation of the treatment cannot be postponed, and 4) presumed innovation (Table 1).[2] In May 2022, criteria 2 and 4 were revised (Table 1).[3]

Table 1. Overview of EA eligibility criteria

Criteria	Assessment criteria/Description	
1) Severe, rare or debilitating disease	• Description of the symptoms and organ involvement • Mortality rate	• Impact of the disease on patients' quality of life • The prevalence and incidence of the disease are used to support its rarity
2) Lack of appropriate treatment	• Appropriate treatment - pharmacological or non-pharmacological therapeutic alternative: • with MA and/or early access or treatment used off-label based on guidelines AND • is accessible in routine practice in France (without supply issues) AND	• is reimbursed by public funding AND • has satisfactory efficacy and safety data to suggest that the patient would lose no potential benefit compared with the predictable benefit of the drug in the EA application
	Refined criteria in May 2022: when a treatment is likely to respond to a health emergency, clinically relevant therapeutic options may not be considered as appropriate treatment	
3) Initiation of the treatment cannot be postponed	Based on whether an appropriate treatment exists or not	
4) Presumed innovation	Three conditions to be fulfilled: • Novel treatment regimen • Suitable development plan and clinical findings supporting a presumptive benefit for the patient • No significant unknowns for safety	**Refined criteria in May 2022:** • 2nd criteria (presumptive benefit part) revised: the presumption of benefit for the patient must be assessed in the context of the existing therapeutic strategy • 3rd criteria replaced by filling an unmet medical need

Source: HAS 2021[2] and HAS 2022[3]

Review of available EA assessments for OD

- As of September 21st, n=24 EA requests for OD were submitted, of which n=23 (96%) were granted (n=8 pre-MA (35%) and n=15 (65%) post-MA) (Table 2).
- Therapeutic indications of approved OD EA included cancer (n=10, 44%), genetic disease (n=9, 39%) and others (4, 17%).
- The average time from submitting an EA request to EA authorization for ODs was 95 and 71 days before and after MA, respectively.

Table 2 Overview of EA request and distribution by therapeutic area

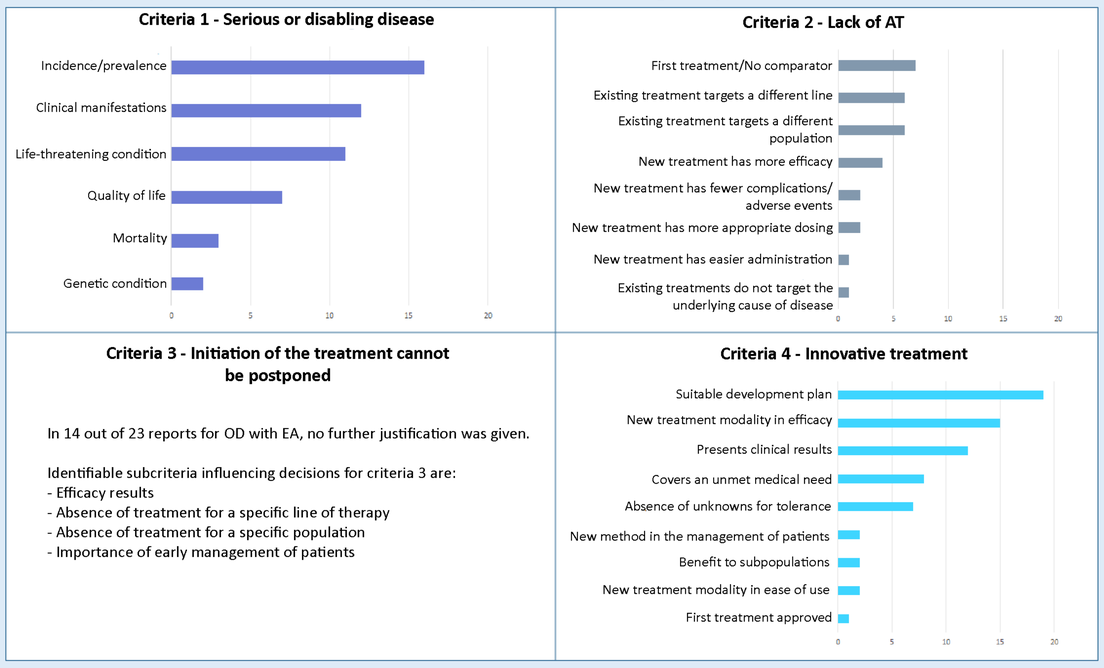
Total EA requests	81	
Total EA refused	10	12%
Total EA granted	71	88%
Total OD EA requests	24	
Total OD EA refused	1	4%
Total OD EA granted	23	96%
Pre MA requested	9	37%
Post MA requested	15	63%
Cancer drugs	10	42%
Genetic disease	9	37%
Others*	5	21%

*Includes autoimmune disease, blood vessel disease, deimmunization treatment for kidney transplants, graft-versus-host disease

Key considerations raised by TC to grant EA for 23 OD are summarized in Figure 1 per criteria. The most cited prerequisites for 1st criteria were incidence/prevalence, clinical manifestations, and life-threatening disease; for 2nd, no treatment approved, or existing treatments are not satisfactory; for 3rd "initiation of treatment cannot be postponed" refers to absence of appropriate treatments (not discussed further in most assessments). For 4th criteria, suitable development plan, new treatment modality in efficacy, and clinical results supporting the presumption of benefit.

Out the 23 EA requests that were granted (of total 24 assessed), 2 (Kimozo, Oxbryta): were initially rejected by TC to be later granted EA by HAS board. Reasons for (initial) rejection by the TC are summarized in Table 3.

Figure 1. Key considerations used by HAS as justification per EA eligibility criteria



% are calculated based on the number of EA applications which cited the respective criteria and the number of EA applications that were granted (N=23)

Table 3 Rationale behind EA request rejections by TC

	Leukotac	Kimozo	Oxbryta
Indication:	Graft-versus-host disease	Neuroblastoma	Sickle cell disease
Reason for EA refusal:	**Criteria 2-4 not met** ▪ Existing appropriate treatments ▪ Not innovative (lack of sufficient magnitude of effect)	**Criteria 3 and 4 not met**: Treatment can be deferred until data uncertainties are resolved ▪ No transposability of results to younger children ▪ No tolerability data from clinical trials	**Criteria 3 not met:** Treatment can be deferred as no strong evidence on clinical benefit ▪ Efficacy not shown through clinical endpoints (only on one biological endpoint - hemoglobin level) ▪ Poor internal validity and high risk of bias of the main clinical study: amendment to the protocol after interim analysis (analysis population and size of trial, primary endpoint definition, modification of all the prioritized secondary endpoints)
Reason for HAS board overruling:	*Not applicable as the treatment was not granted EA*	Absence of appropriate treatment: the new therapy has strongly presumed efficacy and its implementation cannot be postponed. Presumption of innovation: new treatment modality that can bring a substantial change to patients in terms of ease of use.	No appropriate treatment: the new medicine is an innovative treatment for a serious debilitating disease and its implementation cannot be postponed.

Overview of subsequent TC decisions on OD that were in EA program

- Of the n=10 OD under EA subsequently submitted to TC for regular HTA evaluation, n=7 (70%) received an SMR Important, n=2 (20%) received an SMR Important and Insufficient, n=1 (10%) received an SMR Mild and Insufficient (for different subpopulations). The Insufficient SMR in some subpopulations was due to lack of clinical data and the medicines were subsequently not reimbursed in respective indications.
- In terms of improvement in added benefit (ASMR), n=1 (10%) received important improvement (ASMR II), n=4 (40%) received moderate (ASMR III), n=1 (10%) received minor (ASMR IV), and n=4 (40%) no improvement (ASMR V).
- For 7 out of 10 OD, the TC cited data from their EA phase in the regular HTA evaluation. In 4 cases, it was specified that no data was collected or available from EA program. In 2 cases, safety data from EA were described. In 1 case, efficacy data were deemed unusable due to the large number of missing data.

Conclusion

While the TC committee might reject EA for OD due to uncertainty on clinical benefits, HAS board has an opportunity to overrule based on the unmet need, lack of appropriate treatment, and strong presumption of clinical benefit.

Overall, changes in French EA allow pharmaceutical companies to enter through a simplified EA process with clearly specified criteria, particularly for the OD putting them in a better position for TC formal evaluation providing they meet the 4 criteria and have a plan in place to collect RWE.

References

1. *European Federation of Pharmaceutical Industries and Associations (EFPIA). The root cause of unavailability and delay to innovative medicines: Reducing the time before patients have access to innovative medicines. April 2022.*
2. *French National Authority for Health (HAS). Authorization for early access to medicinal products: HAS assessment doctrine. 2021.*
3. *French National Authority for Health (HAS). Early access authorization: a positive initial report and refined assessment methods. 2022.*