ISPOR EUROPE 2025 | GLASGOW, SCOTLAND | 9-12 November 2025

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A Comparative Analysis of Early Access Pathways in Italy and France: Law 648-96 vs the French AAP

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Background

Early access programs (EAPs) allow pre-authorisation or pre-reimbursement access to medicinal products outside the context of clinical research, typically when no valid therapeutic alternatives exist and the condition is serious or life-threatening.
Italy's early access program is regulated by Law 648/96. This legislation allows the National Health Service to reimburse a drug following an opinion from AIFA's Scientific and Economic Commission (CSE) when no valid therapeutic alternative is available. The law specifically provides access under three scenarios: for innovative medicines authorized in other countries but not in Italy (on-label); for medicines not yet authorized but undergoing at least phase II clinical trials (on-label); and for medicines intended for a therapeutic indication different from their authorized one (off-label).
In France, early access programs are regulated under the *Autorisation d'Accès Précoce* (AAP) framework, introduced by the Social Security Financing Law 2021 (LOI 2020-1576). The program covers indications under development, before marketing authorisation (AP1 - *Accès Précoce 1*), extending after marketing authorisation through to completion of pricing and reimbursement (AP2 - *Accès Précoce 2*). Eligibility also requires meeting the presumption of innovativeness (meaning the medicine delivers substantial patient benefit), being supported by a development plan and clinical data, and showing no major unknowns on safety or tolerability.

Objectives

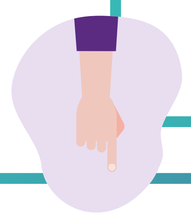
This study compares the two frameworks to:
- Assess their effectiveness in delivering early access to innovative medicines;
- Understand their implications for routine reimbursement.

Methods

We conducted a comparative analysis of early access (EA) requests submitted in Italy and France between 1 January 2023 and 31 December 2024. For each request, we collected information on product type (distinguishing between new active substances, indication expansions, off-label use), as well as whether the product was an advanced therapy medicinal product (ATMP), biological product, and/or orphan product, and the indication. We also captured whether the early access request was accepted, rejected or under review. The timing of the early access decision was categorised as pre-CHMP opinion, between CHMP opinion and marketing authorisation, or post-MA.
In Italy, as the submission date of 648/96 requests is not public, timelines were calculated from their first appearance on the agenda of AIFA's Pre-Authorisation Area. Processing time of both the early access authorisation and, where applicable, routine reimbursement were captured. Lastly, we analysed the relationship between early access decisions and subsequent reimbursement decisions.

Results

In Italy, a total of 126 early access applications were submitted, of which 30 were on-label and 96 off-label, the latter not being comparable with the French AAP framework. Out of the 30 on-label requests, 11 were supported by at least phase II company-sponsored clinical trials, and assumed to be intended to support EMA submission. Among on-label requests, the majority concerned new active substances (73%; n=22), while the rest referred to indication expansions (27%; n=8). In France, 76 requests were assessed, 78% (n=59) related to new active substances and 21% (n=16) to indication expansions. The average EA processing time, for both positive and negative EA decisions, was longer in Italy compared with France 169 vs 114 days. In France, the average time from early access decision to routine reimbursement is 275 days. This includes ~134 days from EA decision to the HAS HTA opinion, followed by ~163 days from HTA opinion to reimbursement. In Italy, products with an EA approval reached routine reimbursement after an average of 498 days. Overall, EA-rejection rates were higher in Italy (70%, n=21) than in France (49%, n=37). Among the cases that subsequently applied for routine reimbursement (n=16) in Italy, reimbursement was granted in 67% (n=4 out of 6) of EA-approved and in 70% (n=7 out of 10) of EA-rejected cases, compared with 27% (n=7 out of 26) and 28% (n=5 out of 18) in France.



Conclusions

The time from EA request to EA decision is slower for the Italian 648/96 process than for the French Early Access Program (169 days vs 114 days). It is likely that the estimate for the Italian 648/96 process is underestimated, given the time between submission date of the 648/96 request and the first appearance on the agenda for discussion with AIFA is not publicly available. The Italian 648/96 process also has a higher rejection rate (70% vs 49%) than the French Early Access Programme. While the likelihood of transitioning to routine reimbursement is similar (53% in Italy vs 58% in France), the absolute number of products transitioning to routine reimbursement in France is significantly higher (44) versus Italy (16). Overall, these findings show that compared to the French AAP, Italy's Law 648/96 is less effective in delivering early access to innovative medicines and supporting timely transition to routine reimbursement.

Bibliography

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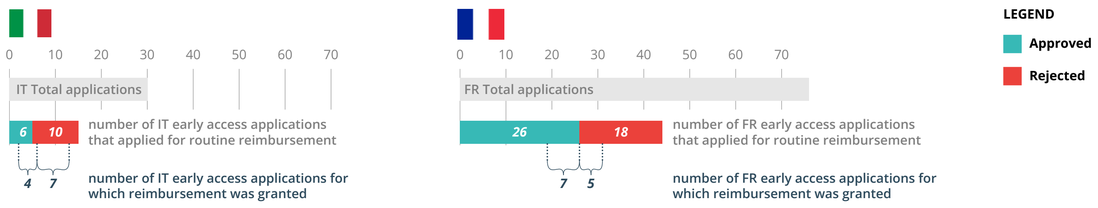
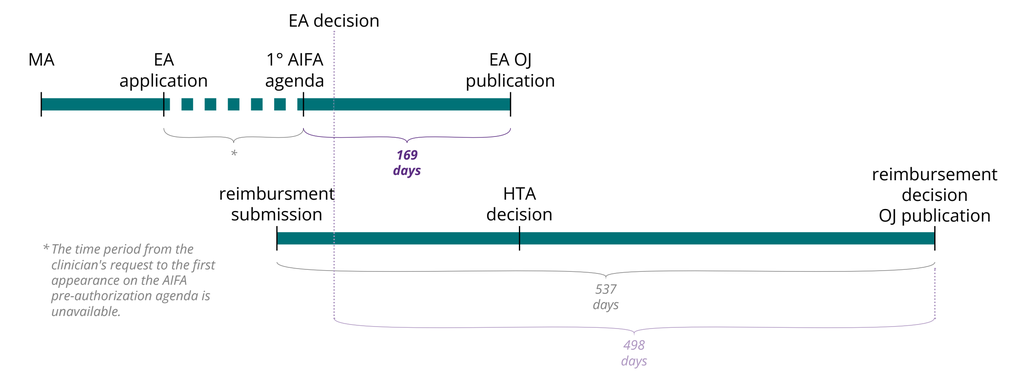
This study was supported by an unconditional grant from Amgen. The sponsor provided input for consideration by the research team; final content and conclusions are the responsibility of the authors.

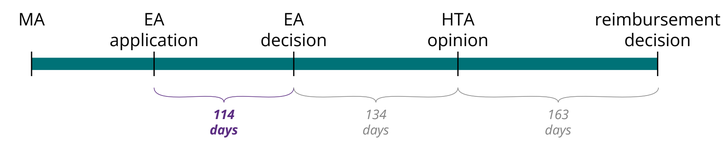
Number of Early Access Applications that applied for routine reimbursement



Timing of *Law 648/96* pathway in Italy



Timing of *AAP pathway* in France



30 Early access requests analyzed for Italy

76 Early access requests analyzed for France