Analysis of the impact of early access on pricing and reimbursement decisions in France

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Background and objectives

- The revised French EA programme was introduced in July 2021 to ensure early access to innovative products before pricing and reimbursement decisions are made
- EA can be requested before or after MA
- For EA to be granted, there must be a presumed positive risk-benefit ratio assessed by the ANSM, and—according to HAS—the following 4 conditions must be met: 1) severe, rare or debilitating disorder; 2) lack of appropriate treatment; 3) impossibility of deferring treatment; and 4) presumed innovation
- The HAS college is the final decision-maker concerning EA requests. The TC evaluates the product's eligibility criteria and shares its preliminary opinion. Then, the HAS college reviews the TC's opinion and provides its final decision. If one of the criteria is not met, the TC's opinion will be unfavourable. However, the HAS college can challenge this opinion and decide to grant EA in specific cases
- This retrospective analysis aims to investigate the impact of EA decisions on pricing and reimbursement in France

Methods

- All EA decision reports published by HAS between 1 July 2021 and 30 April 2023 (the cut-off date for publications) were identified and analysed (1)[a]
  - Extracted information included product characteristics (MA date if available, orphan drug status, and therapeutic area); EA request characteristics (new requests, renewals, and dates); assessments of the eligibility criteria; clinical data submitted; and EA decisions based on ANSM, HAS, and HAS college conclusions
- For all products granted EA, it was assessed whether an HAS opinion for reimbursement (issued by the TC by October 2023) related to the drug listing had been published (2)
  - Extracted information included dossier dates; indication; clinical data submitted; population size; and TC recommendations on SMR, ASMR, and ISP
- A comparative pricing analysis was conducted between EA prices and negotiated list prices using amounts extracted from the French Ministry of Health and health insurance websites (3-5)

Results

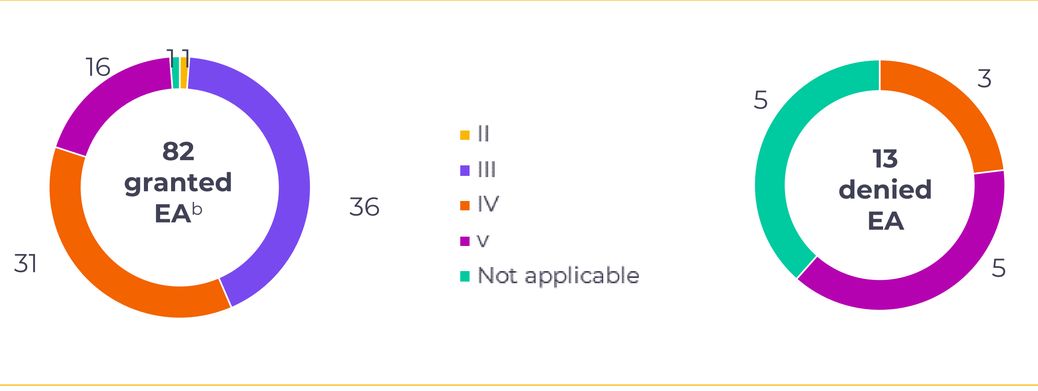
- One hundred forty-two EA decisions related to 90 products were published across a 22-month time frame (1 July 2021 to 30 April 2023). Forty-six products had >1 EA request for different indications or were reassessed in the EA programme
- Among new EA requests (excluding renewals, n=113), 95 TC opinions for reimbursement were published (Figure 1)

Figure 1. Available TC reimbursement opinions following EA decisions

- The results of phase 3, double-blind, randomised studies were submitted for 20% (23/113) of the EA decisions
- Indirect treatment comparisons were submitted in 11% of EA dossiers. ITCs were usually used as supporting information in dossiers where pivotal trials were SATs (75% of cases). HAS did not accept these ITCs mainly because of methodologic limitations (statistical adjustments, naïve comparisons, heterogeneity, and the unanchored nature of matching-adjusted indirect comparisons). Notably, ITCs were not identified as a guarantee nor a negative indicator as to whether or not EA would be granted
- In 75% of cases, the indication submitted for reimbursement was the same as in the EA request; remaining cases targeted a broader indication
- All TC opinions after an approved EA (n=82) were positive except for 1, recognising different levels of clinical (added) value depending on the effect size and the quality of the clinical data submitted to the TC. Most products with an approved EA had important clinical value (73%) (Figure 2)
  - A product with insufficient SMR had initially received a negative opinion from the TC at the time of the EA assessment because treatment could be deferred, but EA was granted by the HAS college as a result of the high medical need and disease severity. At the time of the reimbursement decision, the effect size demonstrated in a non-comparative phase 1/2 trial was considered modest, leading to a negative opinion regarding reimbursement
  - Seven products granted EA were considered to have moderate or weak SMR by the TC because of a low or moderate effect size, safety issues, and/or low-quality data (e.g., immature phase 1/2 results)
  - Clinical added value (major to minor) was recognised in more than 3/4 of the cases. Reported ASMR levels varied depending on the demonstrated effect sizes versus clinically relevant comparators: II to III (44%); IV (37%); and V (19%) (Figure 3)

Figure 2. Distribution of SMR levels after positive or negative EA decisions

Figure 3. Distribution of ASMR levels after positive or negative EA decisions



[b]Two products had more than 1 ASMR value in different subpopulations

- EA denial did not prevent drug reimbursement, particularly in cases where the reason for EA refusal was the availability of appropriate treatments
  - Reimbursement was achieved in 60% of denied EA cases, with 3 products granted minor clinical added value after demonstrating a clinically relevant improvement in efficacy (or superiority) versus an appropriate comparator during TC assessment
  - While limited or uncertain efficacy was the main driver for EA denial, the TC recognised the efficacy (modest or important) of 5 products with denied EA requests in a subpopulation (not the full claimed indication), which led to reimbursement with restriction of indication (e.g., as a fifth-line treatment in 1 case)
  - However, about 40% of products with denied EA requests due to a lack of presumed innovation were not granted reimbursement (SMR insufficient, n=5/13) because of a lack of demonstrated value in the target indication
- Only 5 products had both their EA and list prices negotiated after a TC opinion (Table 1)
- Among these 5 products, 3 were already reimbursed and had available prices negotiated in other indications, limiting the number of relevant products for this analysis
- The 2 products with a first indication, Onureg® (azacitidine) and Voxzogo® (vosoritide), were granted ASMR III and their prices were either decreased by 12% or remained unchanged, respectively
- If the final negotiated price was lower than the price set during the EA programme, manufacturers were required to pay the difference back to buyers (considering that 100% of the product cost was endorsed by the French national health insurance system)

Table 1. Pricing analysis

Parameter	Onureg® (azacytidine)	Keytruda® 25 mg (pembrolizumab)	Voxzogo® (vosoritide)	Kaftrio® (elexacaftor/ tezacaftor/ ivacaftor)	Lynparza® (Olaparib)
Reimbursed for other indications	No	Yes	No	Yes	Yes
TC opinion date	17 November 2021	7 December 2022	15 December 2021	11 May 2022	18 January 2023
SMR	Important	Important	Important	Important	Important
ASMR	III	III and IV	III	II and IV	III
EA price, €	1054.95	2592.59	712.33	175.34	37.46
List unit price, €	928.57	2431.00	712.33	175.34	38.25
Difference, %	**-11.97%**	**-6.23%**	**0%**	**0%**	**+2.11%**

Conclusions

- Because HAS is among the main EA decision-makers, it has access to clinical evidence prior to reimbursement dossier submission. Hence, it represents the first opportunity through which to introduce the product and its potential clinical value
- EA being granted, particularly following a positive TC recommendation, may be a positive indicator of reimbursement, but the recognised clinical value (SMR) and clinical added value (ASMR) depend on several factors, including the effect size and the quality of the clinical data
- EA is granted only for innovative products, providing they meet stringent eligibility criteria. EA denial does not necessarily lead to rejected reimbursement during TC assessment. Achieving reimbursement for the full indication or a subpopulation is feasible if a considered market access strategy is prepared to optimise the demonstration of the product's clinical value
- A 16% price drop was observed before the reform for products granted EA (7). Our analysis reveals that, after the reform, there is no clear price-setting trend following the granting of EA, as most products are reimbursed for other indications
- Price negotiation is a complex process based on multiple factors (clinical added value, population size, and previous reimbursement for other indications). More cases are required to better understand the potential impact of each factor after the reform

[a]At the time of writing, HAS had published an overview of EA decisions with a cut-off date for EA decisions of 30 June 2023; even if the actual figures differed slightly due to cut-off date differences, we identified similar trends (6)

Abbreviations: ANSM, Agence nationale de sécurité du médicament et des produits de santé; ASMR, amélioration du service médical rendu; ATU, autorisation temporaire d'utilisation; EA, early access; HAS, Haute Autorité de Santé; ISP, impact sur la santé publique; ITC, indirect treatment comparison; MA, marketing authorisation; MAIC, matching-adjusted indirect comparison; OD, orphan designation; PR, pricing and reimbursement; PUT-RD, protocole d'utilisation thérapeutique et assurer le recueil des données en vie réelle; SAT, single-arm trial; SMR, service médical rendu; TC, transparency committee

References
1. HAS. https://www.has-sante.fr/upload/docs/application/pdf/2021-06/acces_precoces_-_doctrine.pdf; 2. HAS. https://www.has-sante.fr/jcms/p_3281266/fr/avis-et-decisions-sur-les-medicaments; 3. MSP. https://sante.gouv.fr/ministere/acteurs/instances-rattachees/comite-economique-des-produits-de-sante-ceps/article/autorisations-d-acces-precoce-ex-atu-montants-des-indemnites-maximales; 4. Ameli. http://www.codage.ext.cnamts.fr/codif/bdm_it/index.php?p_site=AMELI; 5. Journal officiel de la République Française. https://www.legifrance.gouv.fr/; 6. HAS. https://has-sante.fr/upload/docs/application/pdf/2023-10/synthese_aap_2ans.pdf; 7. Watt A. https://www.pharmaceutical-technology.com/pricing-and-market-access/early-access-france/?cf-view

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