Relationship between cost-effectiveness threshold and drug reimbursement in Spain, Italy and France

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Background

Health Technology Assessment (HTA) summarises information about medical, economic, social and ethical issues related to the use of a health technology. Economic evaluation is increasingly used in pharmaceutical reimbursement across Europe to inform decision-making in the HTA process[1-4].

A key tool is the incremental cost-effectiveness ratio (ICER), which compares the additional cost and benefit of new medicines, often against a cost-effectiveness threshold (CET) which represents the maximum a health system is willing to pay per additional quality-adjusted life year (QALY).

Objectives

To assess whether incremental cost-effectiveness ratios (ICERs) and cost-effectiveness thresholds (CET) influence reimbursement decisions of medicines in Spain, Italy and France and to explore the extent to which economic evidence drives funding outcomes in practice.

Methods

A review of publications on HTA in Spain, Italy, and France was conducted in order to analyze the CET.

Next, all Therapeutic Positioning Reports (IPTs) published in Spain that included an economic evaluation section were examined. These reports correspond to the period during which the Drug Evaluation Network (Revalmed)-AEMPS program was in effect, specifically between 2021 and 2022[5]. Then, specific ICERs mentioned were extracted when available. Reports with economic evaluation, but without cost-effectiveness, were excluded (those containing cost minimization or budget impact without cost-effectiveness analysis).

The variables of the drugs were described, including orphan drug designation, type of medication number of indications and therapeutic area. Additionally, the ICER obtained in Spain for these subgroups was analyzed.

Then, relevant evaluation reports from Italy (AIFA)[6] and France (CEESP/HAS)[7] of these drugs were analyzed to identify reported ICERs and gather data on the reimbursement status from official sources in each country.

Results

Spain, Italy, and France do not use formal, publicly stated CETs, yet economic evidence still plays a role in decision-making. Studies suggest implicit thresholds of approximately €30,000/QALY in Spain and Italy[8-10] and €50,000/QALY in France[11]. Additionally, in our study we have found that the IPTs cited thresholds ranging from €20,000 to €60,000/QALY. However, reimbursement decisions often depend on multiple factors beyond ICERs, such as clinical benefit, budget impact, and price.

Out of the 19 IPTs found in Spain including economic evaluation section, only 10 included ICER results, developed by Spanish Medicines Agency (AEMPS) or of external reference 5. Of these 10 IPTs, 9 correspond to different treatments, as one treatment has two IPTs (Table 1). In four cases of the 7 reimbursed treatments (57%) the drugs were reimbursed exceeding the CETs.

TREATMENTS	INDICATION	ICER (€/QALY)	Reimbursed status		
		SPAIN	SPAIN	ITALY	FRANCE
Talzenna® (talazoparib)	Patients with HER-2 negative breast cancer with BRCA 1/2 mutations progressing on prior therapies	€ 184,927	No	Yes	Yes
Recarbrio® (imipenem/cilastatin/relebactam)	For the treatment of hospital-acquired pneumonia/VAP with or without bacteremia For the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options	€ 47,311*	Yes, in a restricted label	Yes	Yes, in a restricted label
Edistride® / Forxiga® (dapaglifozina)	In the treatment of symptomatic chronic heart failure with reduced ejection fraction in adult patients	€ 9,406	Yes, in a restricted label	Yes	Yes
Opdivo® (nivolumab)	Monotherapy has been approved for the treatment of adult patients with unresectable advanced, recurrent, or metastatic SCC following prior fluoropyrimidine- and platinum-based combination chemotherapy	€ 793,415	No	Yes, in a restricted label	No
Tukysa® (tucatinib)	Is indicated, in combination with trastuzumab and capecitabine, for the treatment of adult patients with HER-2-positive, locally advanced or metastatic breast cancer who have received at least two prior lines of anti-HER-2 therapy	€ 421,391	Yes	Yes	Yes**
Ontozry® (cenobamato)	Is indicated for the concomitant treatment of focal-onset seizures with or without secondary generalization in adults with epilepsy who have not been adequately controlled despite prior treatment with at least two antiepileptic drugs	€ 24,400	Yes	Yes	Yes
Tecentriq® (atezolizumab)	Monotherapy is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression greater than or equal to 50% on tumor cells (TC) or greater than or equal to 10% of tumor-infiltrating immune cells (IC) and who do not have EGFR mutations or ALK rearrangements	€ 55,354	Yes	Yes	Yes
Jyseleca® (filgotinib)	Is indicated for adult patients with moderately to severely active UC who have had an insufficient response, a loss of response, or have been intolerant to conventional treatment or a biologic medication	€ 4,637	Yes, in a restricted label	Yes	Yes, in a restricted label
Kimmtrak® (tebentafusp)	As monotherapy is indicated for the treatment of unresectable or metastatic uveal melanoma in adult patients with human leukocyte antigen (HLA)-A*02:01 positivity	€ 519,455	Yes	Yes	Yes

* For this treatment, we selected the ICER reported in the second evaluation. - ** ICER (France): 298,148 €/QALY.

Table 1. Evaluated treatments and their reimbursed status

In Spain, seven (78%) were reimbursed (some with restrictions) and two were denied with very high ICERs (Figure 1).

In Italy, all medicines were reimbursed under confidential discount agreements or expenditure caps, but reimbursement decisions did not reference an ICER (Figure 1).

In France, eight were reimbursed (some with restrictions) and one was denied due to lack of therapeutic benefit. Only one included ICER, and this was exceeding the threshold but reimbursed in France (Figure 1).

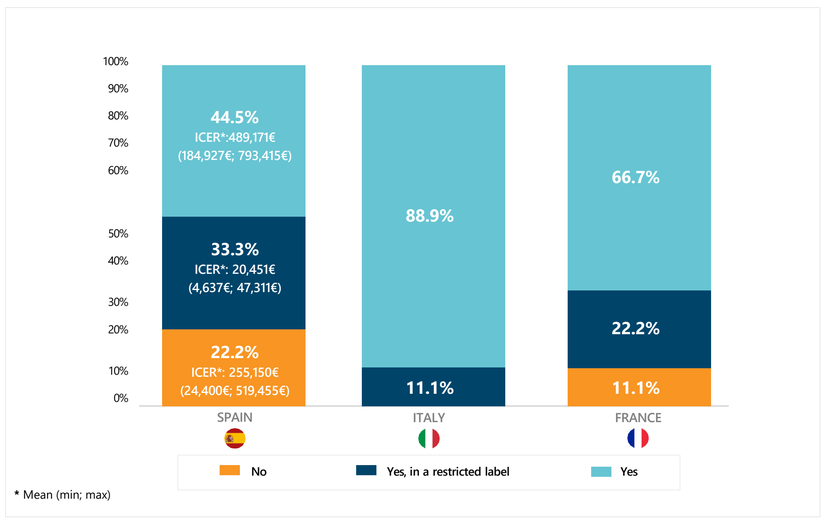

Figure 1. Reimbursement status

Variable	n	%	ICER, mean	n (reimbursed)	ICER, mean (reimbursed)
Type of medications					
Antibiotics	1	11%	€ 47,311	1	€ 47,311
Biologics	2	22%	€ 424,385	1	€ 55,354
Chemical substance	6	67%	€ 194,036	5	€ 195,858
Indications					
New	5	56%	€ 239,497	4	€ 253,139
Drug indication expansion	4	44%	€ 215,703	3	€ 23,132
Therapeutic area					
Oncology	5	56%	€ 394,909	3	€ 332,067
Non-oncology	4	44%	€ 21,439	4	€ 21,439
Orphan designation					
Yes	1	11%	€ 519,455	1	€ 519,455
No	8	89%	€ 192,605	6	€ 93,750

Table 2. Classification of evaluated treatments in Spain

Limitations

The small number of HTAs that include economic evaluation makes it difficult to draw robust conclusions regarding the use of ICER. Additionally, regarding cost-effectiveness analysis, there are limitations arising from the lack of knowledge about the subsidized prices of treatments, which prevents accurate assessment of the real outcomes of published analyses, both in the Spanish context and in other countries.

Conclusion

In general, CETs and ICERs play a limited and inconsistent role in drug reimbursement processes across Spain, Italy, and France, often subordinated to clinical outcomes, budgetary limitations, and negotiation mechanisms. Strengthening transparency and improving the integration of economic evaluations could enhance decision-making processes and promote greater equity in pharmaceutical access within these countries.

New legislation across these three countries might include CETs and ICERs as one of the factors to support decision-making processes.

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