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What drives the limited scope of French National Authority for Health (HAS) economic opinions for rare diseases in France?

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Objectives

The specificities of rare diseases (RD) has led many European HTA bodies to develop specific value assessment frameworks for economic evaluations of orphan drugs.[1] In France, innovative treatments for RD that are expected to have a significant impact on healthcare spending are required to be assessed through a cost-effectiveness analysis (CEA) reviewed by the National Authority for Health (HAS) guidelines.

HAS' assessment of CEA focus on methodological robustness of the methods based on the published guidelines.[2] Methodological reservations (MR) of different levels are assigned depending on the magnitude of uncertainty brought to the analyses by the modelling approaches. A single major MR or too many MR of minor and important level lead HAS to invalidate the CEA, thus excluding its results from the price negotiations.

The nature of RD implies lacking information to model RD's natural history, impact of current standard of care (SoC) and extrapolation of innovative treatments' effects. This frequently leads to HAS expressing MR generating significant uncertainty, limiting the interpretability and scope of its opinion and its potential impact on price negotiations.

We analysed what aspects of CEA were particularly at risk of MR for RD treatments in the context of HAS' guidelines[2] by reviewing economic opinions published by the HAS in 2020 and 2021 for RD treatments and analysed the MR formulated based on an analysis framework, and identified what actions could be implemented to improve the interpretability and significance of economic opinions for French market access.

Methods

We reviewed all economic opinions published by HAS between 2020 and 2021 and identified the ones about RD treatments. Opinions that did not present RD specific challenges such as partitioned survival models in rare cancers were excluded. The selected opinions were then reviewed in the context of HAS' recommendations for CEA main structural choices (Table 1).

Table 1. French requirements for the structural choices in CEAs (HAS guidelines)

Main structural choices	French requirements
Perspective	*Collective perspective that can be restricted to the healthcare system if necessary.*
Modeled Population	*Representative of the analysis population that should be aligned with the population for which reimbursement is requested.*
Comparators	*All clinically relevant comparators.*
Modelling approach & structure	*Should represent the natural history of the disease and the patient management, without introducing more complexity than necessary.*
Effectiveness modelling	*Based on robust comparative clinical data, discussing its transposability to French patients and/or robust indirect comparisons. Extrapolation approaches and results should be justified and validated.*
Time horizon	*Set duration up to lifetime based on a trade-off between including costs and outcomes affected by the impact of comparators on patients' health and limiting the uncertainty associated with long-term extrapolations.*
QoL	*Generic questionnaires (EQ-5D-5L preferred) valued according to French preferences. Validated mapping methods can also be used.*
Costs	*Direct medical costs valued according to production costs.*
Discounting	*Health outcomes and costs discounted at 2.5% per year.*
Validation	*Discussion of internal and external face validity (replication of the clinical data used to parametrize the model and plausibility of modelled outcomes).*

Results

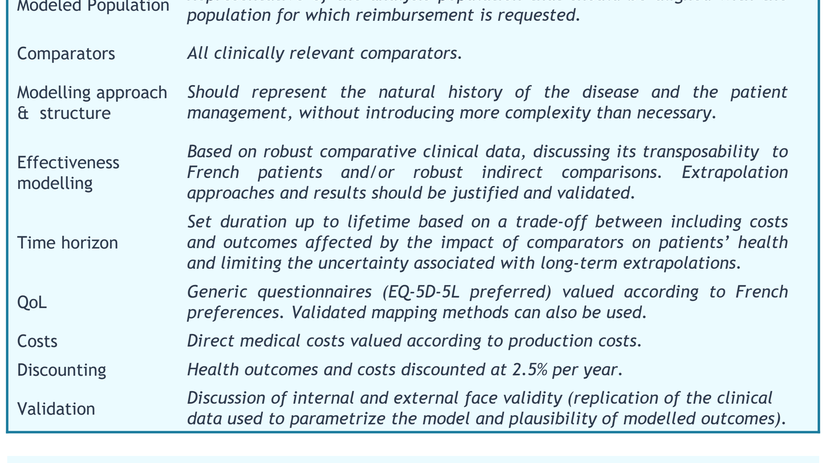
A total of 13 CEAs evaluating RD treatments published in 2020-2021 were identified, representing 26% of all HAS opinions published in the period.

Two opinions for rare cancers were excluded as they relied on partitioned survival approaches fitted to comparative clinical trials with mature results.

ICERS ranged between €50K and €2.5M/QALY. Most opinions reported Cost/QALY ICURs as the main results criteria, Cost/LY ICERs were favored in the case of SMA treatment due to the life-threatening nature of the disease and the age of the modelled population (Figure 1).

Major MR were identified in 3/11 CEAs and the analysis was judged uninterpretable or its scope to be limited by HAS in 10/11 (Table 2). We found no correlation between HAS acceptance and ICER levels (Figure 1).

Figure 1. Incremental Cost-Effectiveness Ratio (ICERs) of CEAs in RD



Almost all dossiers had MR issued for population, modelling of effectiveness, costs & utilities were the most common (Table 3).

Table 3. Sources of MR in rare disease CEAs — *Legend:* Minor MR | Important MR | Major MR

Product	Perspective	Population	Comparators	Model structure	Effectiveness modelling	Time horizon	Costs	QoL	Validity
EVRYSDI	1				5 1			1	1
ZOLGENSMA		1		1	2 4		1	1	1
OXLUMO				1	1 2		1		
KAFTRIO		1			5 2		1	1 2	1
SYMKEVI		1		1	3 1	1	1 1	1 1	
HEPCLUDEX		1 1 1			4 3	1	2	1 2	
VYNDAQEL				1	1 1		1	2	
SOLIRIS	1	1 1	1	1	3	2		1	1
GIVLAARI		1 1	1		3 1		1	1 1	1
EPIDYOLEX		2 2	2	1	3 1		1 3	2 1	2
ZYNTEGLO					2 4	1		1	

➢ *Perspective*

HAS issued one important MR in a dossier where the perspective was limited to the healthcare system as it considered that excluding disability compensation benefits from the analysis was not appropriate in the context of the SMA.

➢ *Population*

HAS issued two important MR regarding the analysis population in cases where disease management and/or SoC determined subpopulations that should have been evaluated independently.

Three important MR and one major MR questioned the transposability of the analysis to French patients in cases where this was considered insufficiently discussed and its impact of the results not properly assessed leading to potential biases.

➢ *Comparators*

In half of CEAs (6/11), the RD treatment was positioned as an add-on to the SoC. HAS issued one major MR due to lacking comparators used in France in the analysis despite the limited possibilities for indirect treatment comparison (ITC).

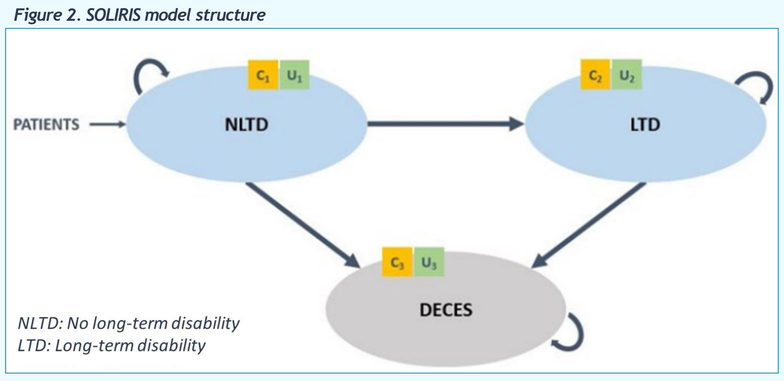
➢ *Model structure*

Most CEAs relied on Markov models (Table 2). Six MR were attributed due to over-simplified or complex structures that did not accurately represent the history of the disease and/or the occurrence of clinical events, treatment effect and resource consumptions.

One important MR was issued concerning a model structure that allowed an unjustified independence between disease severity and patient mortality.

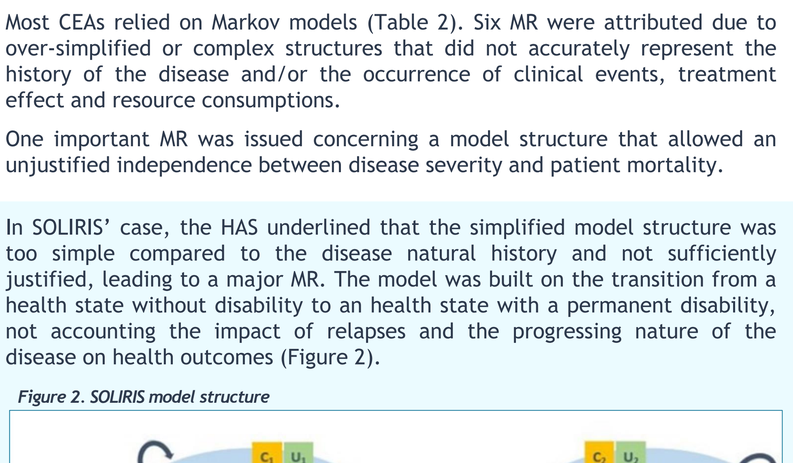
In SOLIRIS' case, the HAS underlined that the simplified model structure was too simple compared to the disease natural history and not sufficiently justified, leading to a major MR. The model was built on the transition from a health state without disability to an health state with a permanent disability, not accounting the impact of relapses and the progressing nature of the disease on health outcomes (Figure 2).

Figure 2. SOLIRIS model structure



In the EPIDYOLEX case (minor MR), the overdetailed model allowed to track costs and QoL of patients but was not suitable for the primary efficacy endpoint of the clinical trials (Figure 3).

Figure 3. EPIDYOLEX model structure



➢ *Modelling of effectiveness*

Lack of real-world evidence and natural history data in the context of RD was a challenge in the majority of cases. This led to 20 minor and 32 important MR in all dossiers due to the estimation of transition probabilities, occurrence of clinical events, or survival extrapolation, often worsened by guidelines absent or that do not reflect the reality of management in the indication, and the lack of expert consensus on the positioning of compared treatments and SoC, especially in contexts were no previous treatment was developed.

Extrapolation of treatment effect beyond the available follow-up was a frequent issue relate to modelling effectiveness. HAS tends to request conservative approaches to model treatment efficacy in the long term, such as assuming no treatment effect or applying a treatment effect waning beyond available follow-up.

➢ *Face validity*

Face validity of long-term extrapolations presented a challenge in the context of many dossiers. Lack of existing data for the modelling of current practice and SoC in the context of RD have led to MR in 6 dossiers. Furthermore, HAS remained critical about the use of non-French data as sources to inform the modelling or validation.

➢ *Time-Horizon*

Given the frequently lacking evidence to model current practice and validate model results, HAS often requests to censor the accruing benefits of treatments by limiting time horizon.

➢ *Impact on the quality of life*

Ten minor and eight important MR highlighted the lack of discussion and justification of the data used, and the lack of robustness of the methodological approaches used to estimate the utilities, with a significant impact on the results. One major MR was issued in the case where a utility increment was associated with the intervention (not conservative and not compliant with guidelines).

Conclusions

In 2020 and 2021, the HAS judged that the majority of CEAs for RD were uninterpretable or their interpretability limited. A total of 61 minor MR, 63 important MR and 4 major MR were issued across the 11 opinions published. These reservations mostly related to the modelled population, model structure, modelling of effectiveness, and the valuation of costs and QoL.

Although the clinical data used were limited and/or immature, the lack of data in the existing indications landscapes represented a major hurdle to the acceptability of CEAs, limiting the accurate modelling of the diseases and the validation of modelled outcomes, especially since in many cases, the populations where treatments demonstrated value and where it was used differed. Additionally, clinical trials allowing cross-over, and emerging innovative treatments in the context of lacking standardised management, both complicated long-term comparisons of treatment effectiveness.

Whereas no ICER threshold is set in France, these caveats limit the interpretability of CEAs for RD submitted to HAS, questioning the relevance of the current general CEA framework and hinting at the need for specific adjustments to assess RD treatments' economic value.

Furthermore, RD treatments being particularly well suited for pre- and post-marketing authorisation early access programmes, manufacturers should leverage theme to generate data to better inform CEAs on existing SoC, positioning of RD treatment and generate real-world evidence on RD treatments' effectiveness.

However, the current French market access pathway, requiring economic evaluation as soon as conclusive clinical results are demonstrated, may not be entirely compatible with this approach. Shifting the market-access calendar, allowing more time to generate real-world and/or long time evidence may represent way to improve the relevance of economic evaluations.

Main findings

Our results advocate for the development of a new economic evaluation framework between the authorities and industry, allowing a better compromise between the necessary methodological requirements and the existing data in the context of RD treatments. This would improve the quality and interpretability of HAS opinions and help leverage health-economic rationale in pricing negotiations.

References

1. Blonda A, Denier Y, Huys I, Simoens S. How to Value Orphan Drugs? A Review of European Value Assessment Frameworks. Front Pharmacol. 2021 May 12.
2. HAS. Choix méthodologiques pour l'évaluation économique. July 2021.

Table 2. Reservations and scope, model structures & time horizons of CEAs in RD

Product	Pathology	Methodological reservations (MR)			Scope of the efficiency opinion	Model structure	Time horizon		
		Minor (-)	Important (+)	Major (++)			Basecase before TE	Basecase after TE	Scenarios
EVRYSDI	SMA	2	8	0	Uninterpretable	*6-state Semi-Markov*	*SMA type I: 10 years SMA type II/III: 40 years*	*SMA type I: 10 years SMA type II/III: 40 years*	*SMA type I: 5 years SMA type II/III: 20 and 30 years*
ZOLGENSMA	SMA	7	4	0	Limited	*6-state Markov*	*Lifetime*	*10 years*	*20 years and lifetime*
OXLUMO	HP1	4	2	0	Limited	*6-state Markov*	*Lifetime*	*Lifetime*	*10 and 30 years*
KAFTRIO	Cystic fibrosis	5	7	1	Uninterpretable and limited	*Microsimulation model associated with a survival model*	*Lifetime*	*40 years*	*10, 20, 30 years and lifetime*
SYMKEVI	Cystic fibrosis	6	6	0	Limited	*Microsimulation model*	*Lifetime*	*Lifetime*	*10, 20 and 30 years*
HEPCLUDEX	HDV	8	8	1	Uninterpretable	*10-state Markov*	*20 years*	*20 years*	*10 years and lifetime*
VYNDAQEL	TCA	3	3	0	Acceptable	*5-state Semi-Markov*	*10 years*	*10 years*	*5 and 15 years*
SOLIRIS	NMOSD	4	6	2	Uninterpretable	*3-state Markov*	*20 years*	*20 years*	*10 years and lifetime*
GIVLAARI	AHP	5	6	0	Limited	*4-state Markov*	*58 years*	*20 years*	*10 years*
EPIDYOLEX	Epilepsy	12	9	0	Limited	*5-state Markov*	*15 years*	*15 years*	*2, 5, 10, 20, 30 and 50 years*
ZYNTEGLO	ß-thalassemia	5	4	0	Limited	*DICE*	*Lifetime*	*Lifetime*	*30 and 40 years*

Abbreviations: AHP: acute hepatic porphyria ; DICE: discrete event simulation model ; HDV: chronic hepatitis D virus infection ; HP1: primary hyperoxaluria type 1 ; NMOSD : neuromyelitis optica spectrum disorder ; SMA: spinal muscular atrophy ; TCA: transthyretin cardiac amyloidosis

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