Exploring Drivers of "Major Global Uncertainty" in Economic Opinions by the HAS

HTA249

Cawston Hélène[1], Ekaputri Maulidia[1], Rattanavong Brenda[2], Gauthier Aline[3]

[1]Amaris Consulting, Paris, France; [2]Amaris Consulting, Montreal, Canada; [3]Amaris Consulting, Barcelona, Spain

AMARIS · CONSULTING ·

INTRODUCTION

- The French Commission for Economic Evaluation and Public Health (CEESP) states in its doctrine that economic evaluations are associated with major global uncertainty (MGU) when:[1]
  1. Uncertainty cannot be assessed qualitatively or quantitatively,
  2. The estimation of key parameters is too uncertain and leading to unstable results,
  3. Several important methodological reservations are made leading to uninterpretable results,
  4. The hypotheses or methodological choices are not plausible given current clinical practice.
- The presence of MGU cancels the guarantee of stability provided in Article 17, thereby impacting pricing negotiation.[2]

OBJECTIVES

- This study aims to review recent CEESP appraisals to identify the main reasons for MGU, and arguments leading to the characterization of MGU in economic opinions.
- Understanding these factors is crucial as MGU impacts pricing conditions in France.

METHODS

- We reviewed all CEESP economic opinions released from the publication of the CEESP doctrine in July 2021, to July 2024.
- We identified appraisals concluding with MGU and extracted the justifications for these conclusions, along with the types and grading of methodological reservations.

RESULTS

Overview of submissions

- Of the 64 economic opinions published since July 2021, 12 (19%) included the MGU qualification.
- 4 were related to COVID-19 indications, 3 related to rare diseases, and 4 had target populations of less than 500 patients/year.
- 7 manufacturers (58%) unsuccessfully challenged the MGU characterization during the contradictory phase [3,5,6,8,9,10,11]

Table 1. Overview of CEESP appraisals subject to MGU

			Level of methodological reservation					
Drug (publication date DD/MM/YY)	Indication	Reported target population	CEA			BIA		
Etranacogene dezaparvovec (06/02/24)[3]	Haemophilia B	320	0	6	3	0	1	1
Onasemnogene abeparvovec (21/11/23)[4]	Spinal muscular atrophy	18	0	8	3	0	2	3
Tixagevimab/cilgavimab (14/03/23)[5]	COVID-19	20% of COVID-19 new cases	0	6	5	0	2	4
Nirmatrelvir/ritonavir (17/01/23)[6]	COVID-19	NA	0	4	3	0	2	2
Semaglutide (13/12/22)[7]	Obesity	799,160 to 1,598,320	0	8	2	1	1	0
Tixagevimab/cilgavimab (30/08/22)[8]	COVID-19	100,000 to 350,000	0	6	5	0	2	2
Nivolumab (30/08/22)[9]	Muscle invasive bladder cancer	1000	0	2	6	0	1	1
Sotrovimab (19/07/22)[10]	COVID-19	20% of COVID-19 new cases	0	9	7	NA		
Imlifidase (24/05/22)[11]	Desensitization treatment of highly sensitized adult kidney transplant patients	184	1	3	2	NA		
Osimertinib (15/02/22)[12]	NSCLC	551	1	5	9	0	2	1
Cabozantinib (14/12/21)[13]	Advanced renal cell carcinoma	6,417	0	5	3	0	1	1
Risdiplam (14/09/21)[14]	Spinal muscular atrophy	1,200	0	13	3	NA		

Abbreviations: BIA: budget-impact analysis; CEA: cost-effectiveness analysis; NA: not applicable

Legend: Minor Important Major

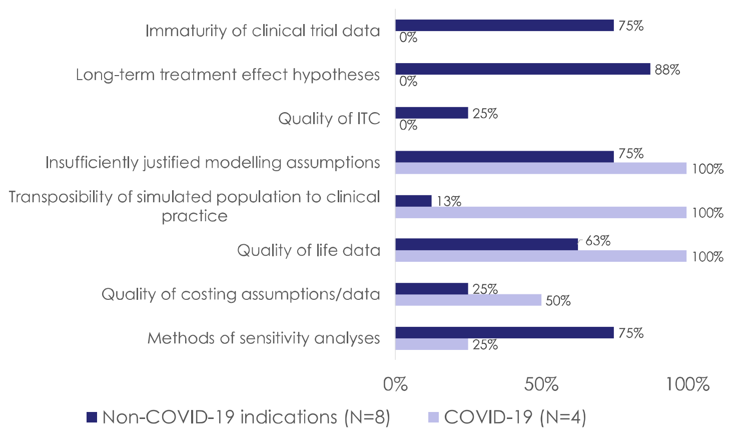
Abbreviations: BIA: budget impact analysis; CEA: cost-effectiveness analysis; NA: not applicable; NSCLC: non-small cell lung cancer; SMA: spinal muscular atrophy

RESULTS

Methodological reservations

- Appraisals with and without MGU had a similar number of major reservations, but those with MGU averaged more important reservations (7.3 vs. 4.0).
- These reservations were most frequently related to modelling aspects of the cost-effectiveness analysis (3.6 important reservations on average).
- For opinions related to non-COVID-19 indications, long-term treatment effect hypotheses was the most frequently mentioned important modelling reservation (88%; Figure 1).

Figure 1. Important methodological reservations



Assessment of uncertainty and rational for major global uncertainty qualification

- In non-COVID-19 indications:
  - In 7 out of 8 opinions (88%), the rationale for the MGU qualification related to a lack or insufficiency of sensitivity or scenario analyses to address sources of uncertainty. [3,4,7,11,12,13,14]
  - In 3/8 opinions,[3,4,11] the base-case result presented by the manufacturer was dominant, while DSA ranges included positive ICERs. In these opinions, the CEESP highlighted non conservative choices in the rational for the MGU qualification
- In opinions linked to COVID-19 indications, the CEESP justified the MGU qualification by the rapid evolution of the epidemiology, the use of strong simplifying hypotheses such as only modelling one pandemic wave, and quality of utility data.

CONCLUSIONS

- The conclusion of major global uncertainty is often linked to data scarcity. Conducting more comprehensive sensitivity analyses could better quantify uncertainty and address CEESP requirements more effectively.

REFERENCES

1. Haute Autorité de Santé. Doctrine of the Commission for Economic and Public Health Evaluation. 2021. https://www.has-sante.fr/upload/docs/application/pdf/2021-09/doctrine_de_la_ceesp.pdf
2. Les Entreprises du Médicament. Article 17, Accord cadre entre le Comité économique des produits de santé et les entreprises du médicament (LEEM). 2021. https://sante.gouv.fr/IMG/pdf/accord_cadre_21-24_signe.pdf
3. Haute Autorité de Santé. Avis économique: HEMGENIX. 2024. https://www.has-sante.fr/jcms/p_3460133/fr/hemgenix-etranacogene-dezaparvovec-hemophilie-b#analyseEco
4. Haute Autorité de Santé. Avis économique: ZOLGENSMA. 2023. https://www.has-sante.fr/jcms/p_3442932/fr/zolgensma-onasemnogene-abeparvovec-amyotrophie-spinale#analyseEco
5. Haute Autorité de Santé. Avis économique: EVUSHELD. 2023. https://www.has-sante.fr/jcms/p_3392499/fr/evusheld-tixagevimab/cilgavimab-covid-19#analyseEco
6. Haute Autorité de Santé. Avis économique: PAXLOVID. 2023. https://www.has-sante.fr/jcms/p_3334227/fr/paxlovid-pf-07321332-/-ritonavir-covid-19#analyseEco
7. Haute Autorité de Santé. Avis économique: WEGOVY. 2022. https://www.has-sante.fr/jcms/p_3398698/fr/wegovy-semaglutide-obesite
8. Haute Autorité de Santé. Avis économique: EVUSHELD. 2022. https://www.has-sante.fr/jcms/p_3352197/fr/evusheld-tixagevimab/cilgavimab-covid-19#analyseEco
9. Haute Autorité de Santé. Avis économique: OPDIVO. 2022. https://www.has-sante.fr/jcms/p_3382948/fr/opdivo-nivolumab-carcinome-urothelial-infiltrant-le-muscle-cuim#analyseEco
10. Haute Autorité de Santé. Avis économique: XEVUDY. 2022. https://www.has-sante.fr/jcms/p_3344400/fr/xevudy-sotrovimab-covid-19
11. Haute Autorité de Santé. Avis économique: IDEFIRIX. 2022. https://www.has-sante.fr/jcms/p_3332338/fr/idefirix-imlifidase#analyseEco
12. Haute Autorité de Santé. Avis économique: TAGRISSO. 2022. https://www.has-sante.fr/jcms/p_3313529/fr/tagrisso-osimertinib-cancer-bronchique-non-a-petites-cellules-cbnpc
13. Haute Autorité de Santé. Avis économique: CABOMETYX. 2021. https://www.has-sante.fr/jcms/p_3294121/fr/cabometyx-20-40-mg-cabozantinib-carcinome-a-cellules-renales-avance-en-association-au-nivolumab#analyseEco
14. Haute Autorité de Santé. Avis économique: EVRYSDI. 2021. https://www.has-sante.fr/jcms/p_3289078/fr/evrysdi-0-75-mg/ml-risdiplam#videotoc_1_1

Presented at: ISPOR Europe 2024; 17-20 November 2024; Barcelona, Spain