

REVIEW OF PUBLISHED EFFICIENCY OPINIONS  
OF THE FRENCH ECONOMIC AND PUBLIC  
HEALTH ASSESSMENT COMMITTEE (CEESP) IN  
CARDIOLOGY AND DIABETOLOGY

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INTRODUCTION

- Cardiovascular diseases represent an important public health issue in France, representing the second cause of mortality (around 30% of the cause of deaths).
- Annually, cardiovascular diseases cause around<sup>1</sup>:
  - 180,000 deaths
  - 130,000 strokes, and
  - 120,000 heart attack.
- Therefore, products belonging to the cardiology and diabetology therapeutic areas constitute a major market in France.
- Since 2013, manufacturers are requested to submit to the French economic and public health assessment committee (Comission Evaluation Economique et de Santé Publique - CEESP) a pharmacoeconomic evaluation for any innovative product claiming a clinical added value (Amélioration du Service Medical Rendu - ASMR) level ≤III with a substantial impact on healthcare expenditures.
- The objective of this study was to review the CEESP efficiency opinions and provide a summary of the methodological concerns (MCs) reported in cardiology/diabetes indications.

METHOD

- All efficiency opinions published by the CEESP until May 2019 were retrieved from the website of the French Health Agency (Haute Autorité de Santé – HAS)<sup>2</sup>.
- For each opinion, the data of interest, such as the therapeutic area, the type of analyses presented, the added clinical benefit claimed and the one obtained, were extracted.
- The MCs raised by the CEESP were also extracted and subsequently classified according to their impact (major, important and minor) and their dimension (e.g. clinical data, programming). The purpose of the concern (e.g. robustness, representativeness) was also extracted.
- The main results were summarised with a focus on the products with cardiology and diabetology indications.

RESULTS

Presentation of the dossier

- 4 opinions related to cardiology and 1 to diabetology were available (Table 1).

Table 1. Summary of cardiology/diabetology opinions

| Product, INN (year)                                    | Indication                                                                                                                                                                                                          | Req. ASMR* | Obt. ASMR |
|--------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------|
| Cardiology                                             |                                                                                                                                                                                                                     |            |           |
| Zontivity®<br>vorapaxar (2015) <sup>3</sup>            | Reduction of atherothrombotic events in adult patients with a history of myocardial infarction, stroke or transient ischemic attacks, co-administered with acetylsalicylic acid and, where appropriate, clopidogrel | III        | Insuff.   |
| Repatha®<br>evoloumab (2015) <sup>4</sup>              | Adults with heterozygous (familial or not) hypercholesterolemia                                                                                                                                                     | II         | IV        |
| Entresto®<br>sacubritil/ valsartan (2016) <sup>5</sup> | Cardiac failure                                                                                                                                                                                                     | II         | IV        |
| Praluent®<br>alirocumab (2016) <sup>6</sup>            | Adults with heterozygous (familial or not) hypercholesterolemia                                                                                                                                                     | III        | -         |
| Diabetology                                            |                                                                                                                                                                                                                     |            |           |
| Jardiance®<br>empagliflozin (2016) <sup>7</sup>        | Uncontrolled type 2 diabetes                                                                                                                                                                                        | III        | IV        |

\* I- major; II- important; III- moderate; IV- minor; and V- non-existent

- All cardiology products applied for a first registration except empagliflozin, indicated in type-2 diabetes, were evaluated for a registration renewal.
- For cardiology products, the results presented were obtained from cohort-level Markov models, while the results presented for empagliflozin were obtained from a discrete events simulation.

Summary of the MCs raised

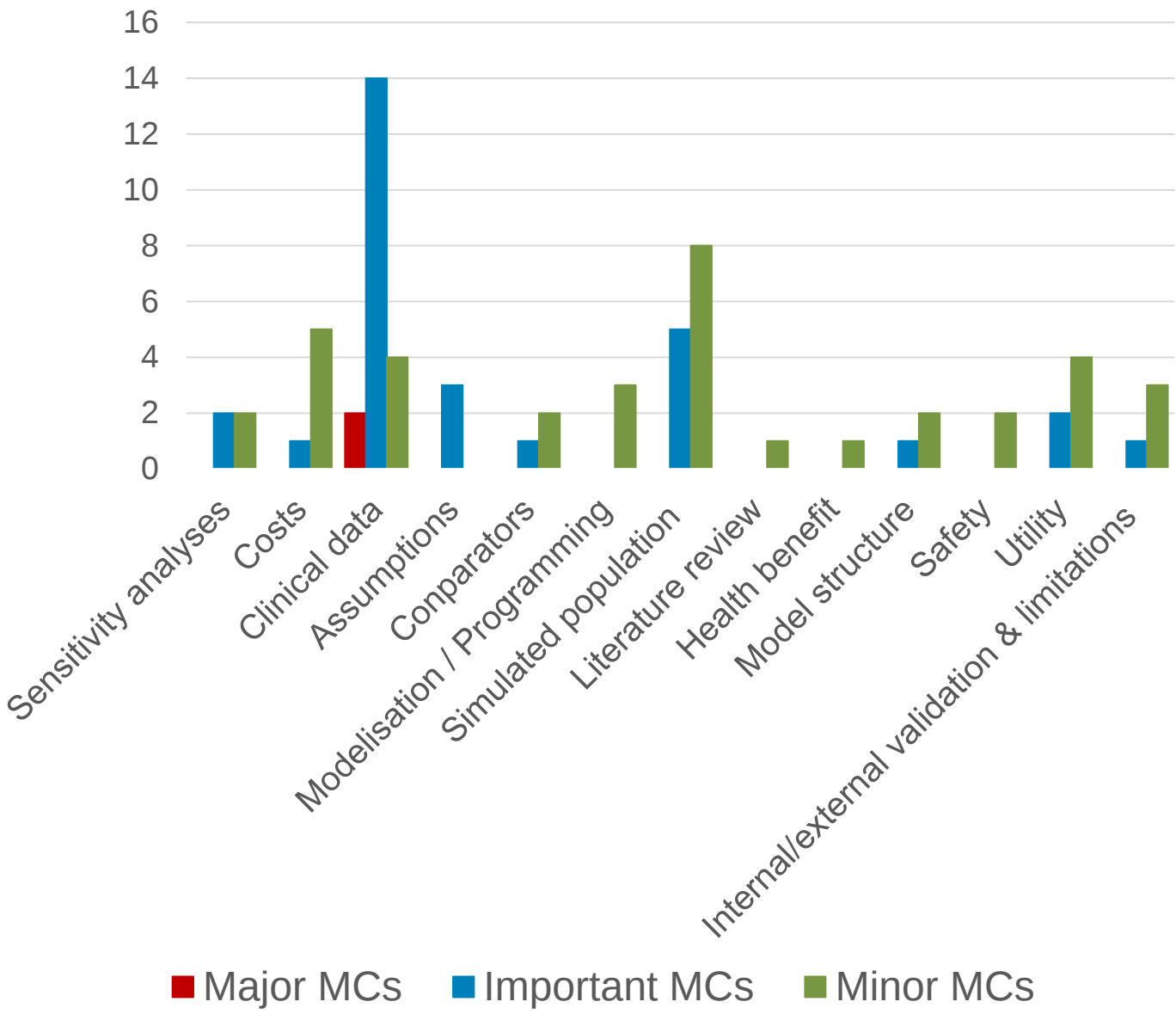
- In the 5 dossiers, a total of 69 MCs were raised (Table 2).

Table 2. MCs raised in the cardiology/diabetology dossiers

| Product    | Major MCs | Important MCs | Minor MCs |
|------------|-----------|---------------|-----------|
| Entresto®  |           | 8             | 8         |
| Praluent®  | 1         | 7             | 13        |
| Repatha®   | 1         | 6             | 6         |
| Zontivity® |           | 6             | 6         |
| Jardiance® |           | 3             | 4         |
| Total      | 2         | 30            | 37        |

- Most of the concerns were related to the clinical data (Figure 1).
- Both major MCs were attributable to the lack of robustness of the clinical data.

Figure 1. Dimension of the MCs raised



- The other main purposes of the concerns were:
  - The estimation method,
  - The uncertainty surrounding the data,
  - The use of surrogate outcomes to estimate treatment effect, and
  - The extrapolation method, with a probable impact on the external validity of the results.
- Numerous concerns were related to the population simulated (13 concerns), especially its representativeness of the French patients (9/13).

DISCUSSION

- In France, authority decision making is much driven by the clinical benefit of the strategy over existing products.
- In such a competitive area, showing an additional health benefit is a key challenge.
  - Thus, the quality and robustness of clinical data appeared to be a crucial aspect of cardiology and diabetology submissions.
- Indeed, among the dossiers studied, all major concerns and half of the important concerns were imputable to the clinical data.
- Any sponsor submitting a dossier in cardiology or diabetology should pay particular attention to the representativeness of the population included their studies and the transferability of the results. Extensive external validation of the model should also be conducted.
- A specificity inherent to this therapeutic area is that the diagnosis and follow-up mainly rely on laboratory test and biological measures.
  - However, it is important for the decision maker to understand how the strategy will effectively impact population health. This has been emphasised in 2 important concerns.
  - The measure of patient-relevant (vs. surrogate) endpoints such as survival or number of cardiovascular events, should be contemplated; or, for lack of such data, validated predictive equations estimating clinical outcomes given laboratory endpoints.

CONCLUSIONS

- Clinical data appeared to be the most frequent dimension of concern, and with the highest impact.
- The most important concern raised were regarding the robustness of the data and the transferability of the results.
- This emphasises the importance of the external validation of the analyses.

REFERENCES

- <https://www.fondationdefrance.org/en/cardiovascular-disease>
- <https://www.has-sante.fr/jcms>
- [https://www.has-sante.fr/jcms/pprd\\_2984295/fr/zontivity-vorapaxar-antiagregant-plaquettaire](https://www.has-sante.fr/jcms/pprd_2984295/fr/zontivity-vorapaxar-antiagregant-plaquettaire)
- [https://www.has-sante.fr/jcms/pprd\\_2983059/fr/repatha](https://www.has-sante.fr/jcms/pprd_2983059/fr/repatha)
- [https://www.has-sante.fr/jcms/pprd\\_2983756/fr/entresto](https://www.has-sante.fr/jcms/pprd_2983756/fr/entresto)
- [https://www.has-sante.fr/jcms/pprd\\_2983646/fr/praluent](https://www.has-sante.fr/jcms/pprd_2983646/fr/praluent)
- [https://www.has-sante.fr/jcms/pprd\\_2982867/fr/jardiance](https://www.has-sante.fr/jcms/pprd_2982867/fr/jardiance)

