Reference Framework, Key Decision-Making Factors, and the Impact of Critical Parameters on Listing Recommendations for Non-Oncologic Drugs for Rare Diseases Issued by Canadian HTA Bodies

HTA283

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INTRODUCTION

The absence of specific Health Technology Assessment (HTA) guidelines for rare diseases remains a limitation in Canada. The decision-making criteria used by Canadian HTA agencies, Institut national d'excellence en santé et en services sociaux (INESSS) and the Canadian Drug Agency (CDA), are not well defined in rare diseases and have been minimally studied to date.

OBJECTIVE

This research aimed to analyze the key decision-making parameters underlying drug listing recommendations for non-oncologic drug for rare diseases (NODRDs) issued by INESSS and CDA from 2020 to 2023, to develop a reference framework for the recommendations of drugs intended to treat rare non-oncologic diseases in Canada.

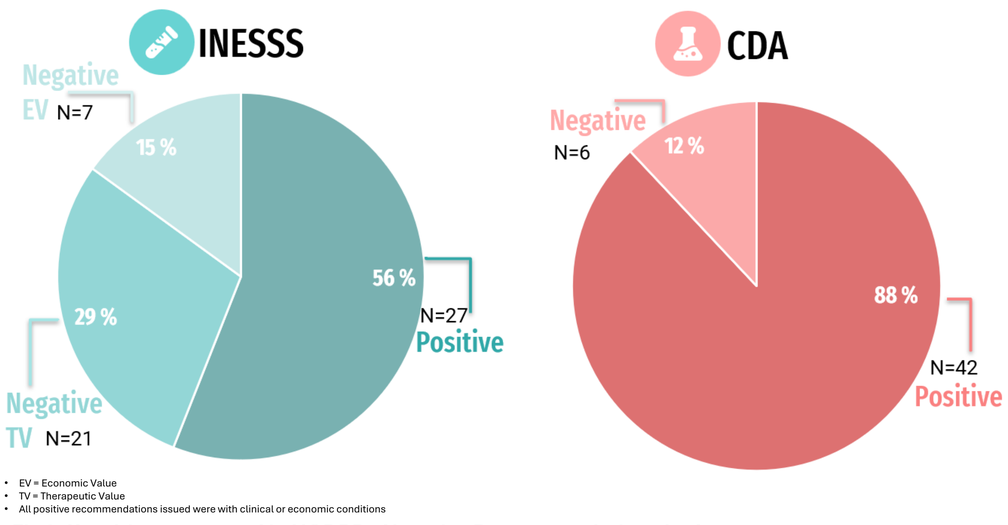
METHOD

A review of the HTA recommendations was conducted for NODRDs (defined as diseases with a prevalence ≤ 1/2,000, based on the Orphanet rare disease registry) for listing recommendations issued between 2020 to 2023 inclusively. Data extraction, synthesis and characterization focused on clinical evidence, pharmacoeconomic outcomes, impact of critical parameters –identified by the lowest rate of positive recommendations when these parameters were absent –key decision-making factors reported by each HTA agency and the outcome of pricing negotiations with the pan-Canadian Pharmaceutical Alliance (pCPA) following positive listing recommendations.

RESULTS

- Among the 48 recommendations issued by each HTA, CDA issued a significantly higher proportion of positive recommendations (88%, n=42) compared to INESSS (56%, n=27) respectively. Overall, this represents 1.6 times more positive recommendations issued by CDA than INESSS. In 40% (n=19) of cases, the two agencies reached divergent conclusions on the listing recommendation of the same drug, with INESSS not recommending reimbursement for the same NODRDs in 89% of those case, although 41% had their therapeutic value recognized, a difference potentially explained by their different legislative framework. (Fig. 1)
- The results of this analysis suggest that parameters with the greatest influence on INESSS's positive listing recommendations, identified by the lowest rate of positive recommendations in their absence, were respectively, the relevance of primary clinical endpoints, the magnitude of the clinical benefit, the type/design of clinical trial and clinician/patient's input whereas the most influential parameters for CDA were clinician/patient's input, the magnitude of clinical benefit, the type/design of clinical trial and the relevance of primary clinical endpoints. (Fig. 2)
- The key predominant decision-making factors reported in INESSS and CDA's negative recommendations were similar, but weighted differently, except for safety and cost-effectiveness considerations as CDA did not refuse any NODRDs for economic reasons or toxicity. Other than the clinical benefit, factors such as quality of the clinical trial, long-term data availability, cost/efficiency, and safety were reported more importantly in INESSS's negative recommendations, whereas the ability to address the unmet medical need appears to be a key decision driver with greater impact on CDA's negative recommendations. (Fig. 3)
- More than half of the NODRDs files submitted to Canadian HTAs involved drugs with an annual treatment cost exceeding $ 200,000. Among the twenty-one (21) negative recommendations issued by INESSS, 14% (n=3) concerned drugs with an annual per-patient treatment cost above $ 1 million. In contrast, the CDA did not issue any negative recommendations for drugs with an annual per-patient treatment cost exceeding $1 million. (Fig. 4)

Fig 1. Proportion of NODRDs Listing Recommendations by Agency

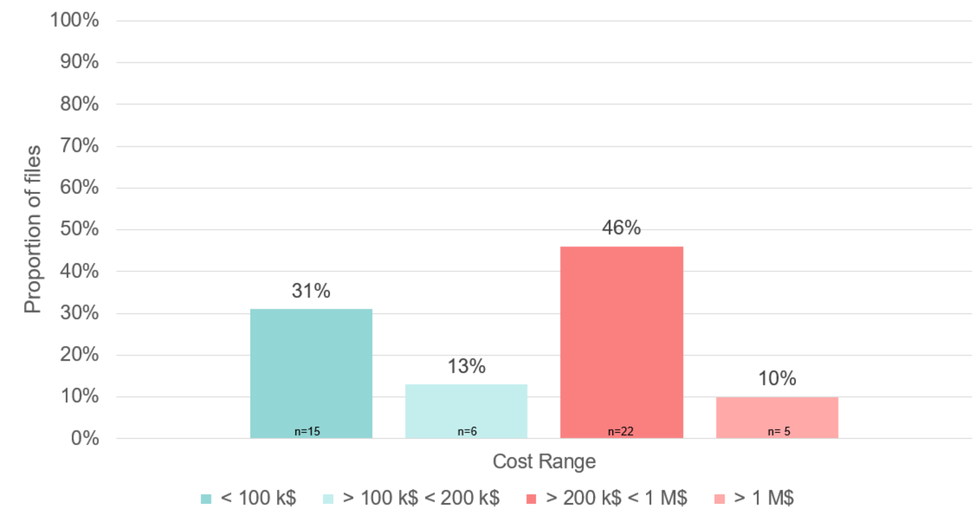


- EV = Economic Value
- TV = Therapeutic Value
- All positive recommendations issued were with clinical or economic conditions

Fig 2. Proportion of NODRDs Positive Recommendations in the absence of critical parameters by Agency

Fig 3. Key drivers reported in NODRDs Negative Recommendations by Agency

Fig 4. Proportion of NODRDs files submitted to Canadian HTAs per cost range



DISCUSSION AND CONCLUSIONS

- The results of this Canadian comparative analysis highlight significant differences in decision-making between the two agencies. However, these results should be interpreted with caution, considering the distinct evaluation processes and different legislative frameworks of INESSS (province of Quebec) and the CDA (rest of Canada). Accordingly, these findings could result from the different values, preferences, roles as well as different evaluation and legal frameworks, among the two Agencies.
- When looking at the four parameters with the greatest influence on the Canadian HTA's positive recommendations, numerically, the observations from this analysis suggest that INESSS may places greater emphasis on the relevance of primary clinical endpoints whereas CDA, on clinician/patient input. (Fig.2) Given that all drug submissions with recognized therapeutic value that initially received a negative recommendation from INESSS were subsequently granted a positive listing decision by the Ministry, it can be inferred that these negative recommendations were primarily driven by economic considerations, as they were ultimately resolved through successful price negotiations. Under Quebec legislation, INESSS is required to first assess a drug's therapeutic value before evaluating additional critical criteria, including price accuracy, cost-effectiveness, the anticipated impact of listing on public health and the healthcare system, and the relevance of listing with the objectives of the public drug insurance plan.
- Although that negative recommendations issued by INESSS that were driven by economic factors could be resolved by a successful negotiation, CDA still issued 1.3 times more positive recommendations than INESSS (when considering both positive and economic value negative recommendations). Nevertheless, the findings could support the need for adaptative HTA processes that bridge clinical, economic, and policy considerations, particularly in the context of high-cost, evidence-limited therapies for rare diseases as only 71% of positive recommendations led to successful pCPA negotiations, underscoring a critical disconnect between HTA outcomes and patient access in Canada.

LIMITATIONS

This analysis remains subject to information bias. The results presented were calculated based on the information available and reported in the agencies' recommendations without conducting comparative statistical analysis. Limitations also arise when interpreting the observed differences between the two agencies, given their distinct evaluation processes. INESSS operates within a legislative framework that mandates the assessment of drugs for listing purposes and the issuance of recommendations to the Ministry. In contrast, CDA, which is neither governed by specific legislation nor directly subject to federal oversight, conducts health technology assessments independently to inform and guide access decisions across Canadian provinces and territories. Consequently, while comparative findings may reveal certain trends in the factors influencing recommendations, they remain inherently constrained by the differing contexts in which Canadian HTAs function and by the distinct legal and regulatory frameworks defining their roles and responsibilities. Therefore, this analysis does not permit definitive conclusions regarding actual differences between the agencies. In fact, access disparities should ideally be assessed based on reimbursement levels across provinces rather than solely on comparisons between INESSS and CDA recommendations.

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DISCLOSURES

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