Consistency in Reimbursement Decisions for Pediatric Rare Disease Drugs at Canadian HTA Agencies: CDA versus INESSS

HTA80

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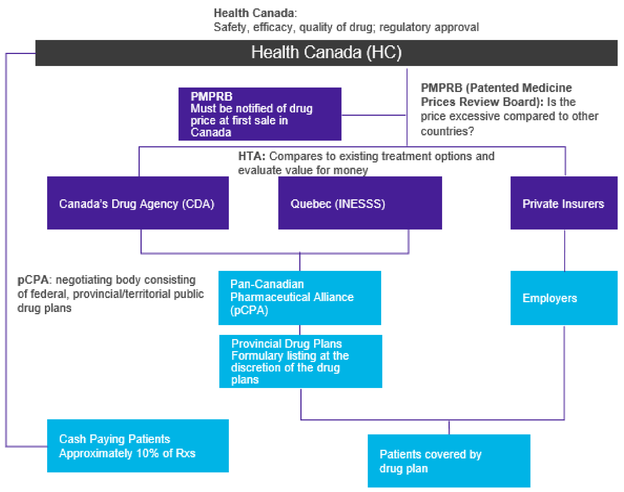
INTRODUCTION

- In Canada, market access for pharmaceutical products start with an approval by Health Canada, followed by a health technology assessment (HTA) process.
- Canada's Drug Agency (CDA) makes reimbursement recommendations that are considered by provincial and federal plans, with the exception of Quebec, where Institute National d'Excellence en Santé et en Services Sociaux (INESSS) issues recommendations to the Regie d'assurance maladie Quebec (RAMQ). Figure 1 shows the dynamic of these organizations.
- It is important to understand the differences between these two agencies with respect to reimbursement decisions, which may provide strategic insights for drug manufacturers and industry professionals.

Figure 1: Canadian regulatory and reimbursement pathways



OBJECTIVES

To investigate drug submissions to CDA and INESSS from 2015 to 2024 in the area of pediatric rare diseases, to identify areas of inconsistencies in reimbursement recommendations.

METHODS

- Using our proprietary CDA Forecaster® database, we examined the recommendations by both agencies and compared recommendation positivity and congruence for all drugs for pediatric rare diseases (age <18 years) which have been reviewed by CDA and INESSS from January 1, 2015, up to December 31, 2024.
- The definition of rare disease was based on the widely used definition from the Canadian Organization for Rare disease (CORD), i.e. conditions affecting less than 1 in 2,000 people.[1]
- The rationale for differences in recommendations by the two agencies was analyzed, and any commonalities were identified.

RESULTS

- A total of 1072 recommendations was identified from CDA during the 10-year review period.
- Of these, 48 were considered rare pediatric diseases, i.e. children under 12 or adolescents under 18 years of age (Figure 2).
- Nearly a quarter of submissions had discordant decisions, in all cases, INESSS refused to reimburse the drug, while CDA recommended conditional reimbursement (Figure 3).

Figure 2: Total number of CDA recommendations in the 10-year period

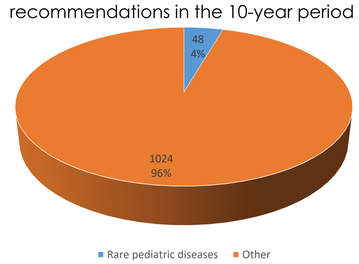
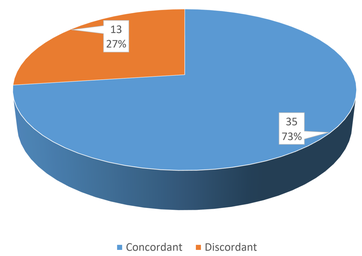
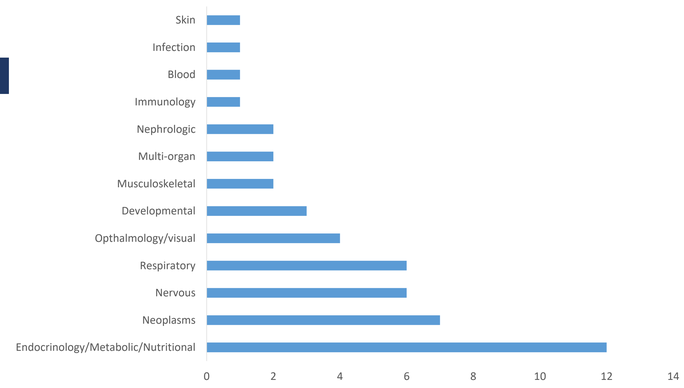


Figure 3: Concordance between CDA and INESSS recommendations



- Most common drugs were for endocrinology/metabolic conditions, followed by various neoplasm, nervous and respiratory system disorders (Figure 4).

Figure 4: Therapeutic class of drug submissions reviewed



AREAS of DISCORDANCE

- 13 (out of 48) pediatric rare disease submissions were identified in which the two agencies had discordant recommendations
- In all cases, INESSS refused listing whereas CDA recommended reimbursement.

Table 1: Reasons for refusal to list medication by INESSS

Indication	Reasons for INESSS to refuse reimbursement
Urea cycle disorders	Cheaper alternative treatment available, which was not modeled in economic analysis.
Urea cycle disorders	Refused unless cost is reduced. Clinical efficacy recognized despite done in observational studies.
Spinal Muscular Atrophy	Initially refused for all subtypes, due to methodological limitations. Later listed for one subtype since therapeutic value was recognized. Separate submission done for other subtypes was approved later.
Lysosomal acid lipase deficiency	One natural history study submitted, and one phase 3 study with methodological limitations.
Corneal cystine crystal deposits	Methodological limitations; drug with the same active ingredient excluded from comparator, although the comparator requires administration every 1-2 hours.
Prevention of hereditary angioedema	Initially refused for lack of long-term data for a new drug class, efficacy assessed in placebo trial despite alternative treatments available. However, therapeutic need was recognized a subgroup of patients. Later submission was revised to these subpopulations, which was accepted, with the addition of long-term data.
X-Linked Hypophosphatemia	Both pediatric and adult submissions refused, due to not including less severe patients, safety concerns, lack of long-term or QOL data, lack of use of main outcomes in practice. While the alternative treatment required multiple doses per day even at night, the trial showed a 95% compliance, which was noted as higher than usual.
Severe primary insulin-like growth factor-1 deficiency	Non-comparative study with a crossover design, no data on long-term growth or QOL. A subset of patients noted as more relevant, but no data provided separately.
Growth hormone deficiency	Trial was methodologically strong and showed noninferiority with less frequent dosing. However, availability of several alternatives, safety concerns, and requiring higher than normal dose led to refusal.
Pompe disease	Despite recognizing unmet need, refused as pivotal trial only showed noninferiority, included treatment-naïve population only, primary outcome was not a functional one, with no reported MCID.
Primary hyperoxaluria type 1	Despite recognizing unmet need, refused due to methodological limitations, although reimbursement criteria was proposed in the event the drug was reimbursed, with suggestions made for RWE and future submission.
Fibrodysplasia Ossificans Progressiva	Despite significant health need, evidence consisted of non-comparator trial with external control, primary outcome affected by outliers, no improvements in some key secondary and QOL outcomes, and safety concerns.
Severe persistent asthma	Short-term data, high cost, and results varied from one study to another particularly in the severely affected population.

MCID: minimum clinically important difference; QOL: quality of life; RWE: real-world evidence

CONCLUSION

- A variety of drugs for rare pediatric diseases were reviewed by CDA and INESSS in the last 10 years.
- Reimbursement decisions overlapped three-quarters of the time.
- INESSS appeared to be more restrictive than CDA in making reimbursement decisions.
- Only 2 INESSS submissions were refused due to economic reasons, the rest due to lack of therapeutic benefits.
- A common reason for refusals was methodological limitations, including one or more of the following: short duration, lack of long-term data, uncertainty between surrogate and more visible clinical outcomes, and lack of use of appropriate comparator.
- Other notable reasons for refusal included non-comparative trial design, lack or indeterminate quality-of-life data, lack of appropriate comparator or patient population, and safety concerns.
- In some cases, the health and unmet need was significant, with no available treatment option. INESSS recognized a more specific patient population in some cases and suggested a resubmission.
- It is expected that the findings from this research will provide valuable insights into the key focuses of the two HTA agencies, particularly where disagreements exist in reimbursement decision.

REFERENCES

1. Canadian Organization for Rare Diseases. "About CORD Key Facts." Retrieved December 30, 2020 from: https://www.raredisorders.ca/about-cord/

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