Can Standard Health Technology Assessment Approaches Help Guide the Price of Orphan Drugs in Canada? A Review of Submissions to the Canadian Agency for Drugs and Technologies in Health Common Drug Review

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Abstract: Orphan drugs have high acquisition costs and when standard health technology assessment (HTA) approaches are used to assess their cost-effectiveness, they often appear not cost-effective. The Canadian Patented Medicine Review Board (PMPRB), through new regulations, will apply HTA assessment results from the Canadian Agency for Drugs and Technologies in Health (CADTH) and Institut national d’excellence en santé et en services sociaux (INESSS) when setting the maximum price that can be charged for Category 1 patented medicines (treatments with an annual cost exceeding 150% of GDP per capita of Canada or with expected annual market size >$50M). Through these regulations, PMPRB has also established a willingness-to-pay threshold of CAD$200,000 or CAD$150,000 per quality adjusted life year (QALY) for medications with a prevalence of no more than 1 in 2000 across all approved indications. We reviewed the orphan drug submissions made to CADTH’s Common Drug Review (CDR) January 2015–May 2020 to understand how the methodology of assessing cost-effectiveness of orphan drugs has guided pricing in Canada. A total of 35 orphan drug submissions were assessed by CDR in this period, none of which met the willingness-to-pay threshold of CAD$50,000 per QALY. Only one drug met the CAD$200,000 per QALY for Therapeutic Criteria Level I, and two drugs met CAD$150,000 per QALY for other Therapeutic Criteria Levels proposed by PMPRB. Price reductions of 32–99% were recommended for treatments that were approved in order to be listed for reimbursement. This review showed that the new PMPRB regulations could be creating challenges for manufacturers of rare disease treatments to meet Canadian pricing regulations. These regulations may jeopardize the launch of new medicines and limit opportunities to add to the development of real-world evidence of orphan drugs, which can be used in reimbursement approaches such as pay-for-performance.

Keywords: orphan drugs, rare diseases, CADTH, QALY, HTA

Introduction
Rare (or orphan) diseases are clinical conditions with very low prevalence. Definitions of rare diseases vary. Health Canada, the European Commission, and United Kingdom Department of Health, refer to any condition that affects fewer than 5 people per 10,000 individuals as a rare disease,¹−³ whereas the United States Food and Drug Administration (US FDA) defines any clinical condition as a rare
The US FDA provides orphan drug status to any drug intended to treat a disease or a condition that affects fewer than 200,000 people in the US, or that affects more than 200,000 persons, for which there is no reasonable expectation the cost of developing and making it available, will be recovered from sales. European Medicines Agency (EMA) provides orphan drug designation to any medicine intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating and with a prevalence not more than 5 in 10,000 in the EU or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development.

Commercial drug development for rare diseases is challenging, particularly due to factors such as low disease prevalence, heterogeneity in the patient populations, limited knowledge of the natural history of the disease, and difficulties in conducting clinical trials because of low patient recruitment, which in turn leads to high research and development costs, and therefore high drug acquisition costs, often making them appear less favorable to payers. Several countries have therefore enacted legislations to incentivize commercial drug development for rare diseases. However, health technology assessments (HTA) with economic evaluations to assess the cost-effectiveness of orphan drugs continue to serve as the main tool to aid reimbursement decisions. Standard HTA approaches include using incremental cost-effectiveness ratios (ICER), thus with the high acquisition costs, orphan drugs tend not to appear cost-effective in a vast majority of the cases, even if they are very effective in treatment of patients compared to the standard of care. Because of the rarity of the disease, drug development costs have to be recovered from a very low number of patients, and the low disease prevalence makes rigorous randomized controlled trials difficult in order to make a compelling case with clinical evidence favoring the product.

To address the issues with conventional HTA processes for orphan drugs, several countries have instituted specialized processes to review these therapies, in which they consider not only cost-effectiveness but also unmet need and severity of the disease. Even when these factors are considered, there is still substantial uncertainty in the orphan drug appraisal process, when only quality adjusted life years (QALYs) are considered as the measure of health benefit and hard cost-effectiveness thresholds are set.

The Canadian government has recently enabled economic evaluations in the HTA submissions to be used as a price regulation tool through amendments to the federal Patented Medicines Regulations. These amendments will allow the Canadian Patented Medicine Review Board (PMPRB), a quasi-judicial federal agency, to apply HTA assessment results by the Canadian Agency for Drugs and Technologies in Health (CADTH) and Institut national d’excellence en santé et en services sociaux (INESSS) when setting the maximum allowable price that can be charged for Category I patented medicines, which are defined as treatments with a 12-month treatment cost exceeding 150% of GDP per capita of Canada or with expected annual market size > $50M. Almost all treatments for Rare diseases in Canada will be classified as category I. According to the most recent guidelines released by PMPRB, a three-step approach is used to set the price of new medicines in Canada. In the first step, at introduction of the new patented medicine, an interim Maximum List Price (iMLP) is set to the median international ex-factory list price of 11 comparator countries for which the patentee has provided information, this iMLP will be valid for three years from the date of introduction of the new patented medicine in Canada. As a second step, when the patentee files international prices, the iMLP is replaced by Maximum List Price (MLP). For category I medicines, as a third step, a Maximum Rebated Price (MRP) is calculated from the iMLP/MLP, this process takes into account the scientific information including therapeutic effect and QALY gain of the new medicines by classifying them into four Therapeutic Criteria Levels (TC Level I–IV) with highest QALY gain expected for Level I and no QALY gain expected for Level IV. For TC Level I, a pharmacoeconomic value threshold (PVT) is set at CAD$200,000 per QALY, the price of the new medicine at this threshold is the pharmacoeconomic price (PEP), the MRP for this level is calculated as 20% off MLP. For TC Levels II, III, and IV the PVT is set at CAD$150,000 per QALY and the MRP is set with a reduction of 30%, 40% and 50% of the MLP, respectively. Additionally, in cases where the expected sales of the new medicine are >50M per year, then the MRP is adjusted with an additional 25%-35% off the MRP calculated using PVT.

Through its new regulations, the PMPRB has apparently established a willingness to pay threshold for treatments with small patient populations and the threshold is the same for treatments of rare and ultra-rare conditions. This study reviews the orphan drug submissions made to
CADTH CDR from January 2015 to March 2020 to examine the economic evidence and the pricing conditions for reimbursement of drugs for rare diseases and also to understand if the methodology of assessing cost-effectiveness of orphan drugs would be helpful to guide pricing in Canada.

Methods
We conducted a targeted review of the CADTH Common Drug Review (CDR) database to identify all the drug submissions between January 2015 and May 2020. In this review, we have included all the drugs classified as orphan drugs based on the diseases or conditions they were indicated for and also by searching the US FDA Orphan Drug Designations and Approvals database for orphan drug status. For all the included rare disease drugs we reviewed, recommendation, pharmacoeconomic and patient group input submission reports as available. For each of the drugs included in the review, data were extracted for drug name, brand name, indication and presence of Health Canada approved treatment alternatives. Additionally, for all the included drugs, annual drug costs, type of economic model, time horizon, comparator, manufacturer base case incremental cost–utility ratio (ICUR), CADTH revised base case ICUR, recommended price reduction, cost-effectiveness thresholds, and recommendation status data were extracted.

Results
We identified 35 submissions of drugs for rare diseases (orphan drugs) that have been assessed by CDR for the study period (Table 1). The 35 orphan drug submissions assessed belong to 31 unique drugs, these drugs are indicated for 24 unique conditions. Most of the drugs assessed were compared to best supportive care (BSC) in their assessments, while eight drugs were compared to active treatments. Thirteen of the drugs assessed did not have treatment alternatives for the indications of interest, and only 5 drug submissions included indirect treatment comparisons. CADTH CDR generally used two cost-effectiveness thresholds, CAD$50,000 per QALY and CAD$100,000 to suggest price reductions in order to approve the drugs for reimbursement. However, for one drug (nusinersen) CADTH CDR used CAD$400,000 per QALY threshold for the recommendation of price reduction. Out of 35 orphan drug submissions, 30 drugs were recommended by CADTH’s Canadian Drug Expert Committee (CDEC) to be listed for reimbursement when clinical conditions and suggested price reductions are met.

Annual Drug Costs
Five of the drugs assessed by CADTH CDR did provide confidential information about the annual drug costs per patient that was not publicly available. Of those drugs that provided this information, the annual drug costs per patient ranged from $4565 (glycerol phenylbutyrate) to > $1M (asfotase alfa).

Cost–Utility Analyses
Twenty-nine submissions used a cost–utility analysis (CUA). Cost–Utility Analyses data for the drugs reviewed are presented in Table 2, out of 29 CUAs, 26 submissions used a Markov model, 2 used micro-simulation approach, and 1 used decision tree. While a majority of the models used a lifetime horizon, few submissions included time horizons in the range of 1 year to 80 years.

For the drugs that reported incremental cost-utility ratios (ICURs) for manufacturer’s base case, none of them met the willingness to pay (WTP) threshold of CAD$50,000 per QALY set by CADTH and the manufacturer’s base case ICUR ranged from $62,794 per QALY (adalimumab) to $6284, 086 per QALY (glycerol phenylbutyrate). CADTH identified several limitations in the model parameters and the data included for each of the submissions. Their subsequent reanalysis of the base case also resulted in higher ICUR for nearly all of the drugs assessed, with revised ICURs ranging from $149,197 (nitisinone) to $24.3 million (nusinersen). Several scenarios analyses were conducted by manufacturers and CADTH CDR, and in general for several of the drugs, scenario analyses resulted in higher ICURs and did not meet the WTP of CAD$50,000 per QALY.

CADTH CDR noted that the majority of the drugs had several uncertainties in the economic data presented, especially in the long-term clinical efficacy of the drug, and the choice of model parameters. Despite the stated uncertainties, 28 drugs were recommended for reimbursement pending a price reduction.

Cost-Consequence and Cost-Minimization Analyses
Three drug submissions (sodium phenylbutyrate, taliglucerase alfa, and lomitapide) presented data from a cost-consequence analysis (CCA). CADTH CDR noted several limitations with the comparative efficacy and safety of the reported data for these interventions, and two of the drugs (taliglucerase alfa and lomitapide) were not recommended for reimbursement. Additionally, three drug submissions
Table 1 Drugs for Rare Diseases Assessed by CADTH CDR (January 2015–May 2020)

| Drug                      | Brand Name  | Indication                                                                 | Health Canada Approved Treatment Alternatives                                      |
|---------------------------|-------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Burosumab20               | Crysiva     | X-linked hypophosphatemia                                                    | None                                                                             |
| Tafamidis11               | Vyndaqel    | Transthyretin amyloid cardiomyopathy                                         | None                                                                             |
| Inotersen22               | Tegedi      | Hereditary transthyretin amyloidosis                                         | None                                                                             |
| Teduglutide23             | Revestive   | Pediatric short bowel syndrome                                               | None                                                                             |
| Lanadelumab24             | Takhtyroz   | Hereditary angioedema                                                        | None                                                                             |
| Patisiran25               | Onpattro     | Polyneuropathy in Transthyretin-mediated amyloidosis                          | Cinyr-eze, Berinert, Firazyr, Haegarda, Tegedi                                    |
| Telotristat26             | Xermelo     | Carcinoid syndrome                                                          | Sandostatin                                                                     |
| Cysteamine27              | Cystadrops  | Corneal cystine crystal deposits                                              | Procsybi                                                                        |
| Cerliponase alfa28        | Brineura    | Neuronal Cereoid Lipofuscinosis type 2                                       | None                                                                             |
| Nusinersen29              | Spinraza    | Spinal muscular atrophy                                                      | None                                                                             |
| Sebelipase alfa30         | Kanuma      | Lysosomal acid lipase deficiency                                              | Orasemogem abeparvoe                                                            |
| Nitisinone31              | Nitisinone  | Hereditary tyrosinemia type 1                                                | Orfasdin, MK-Nitisinone                                                         |
| Nitisinone32              | MDK-Nitisinone | Hereditary tyrosinemia type 1                                            | Orfasdin, Nitisinone                                                            |
| Nitisinone34              | Aczemra     | Giant cell arteritis                                                         | None                                                                             |
| Nitisinone35              | Orfasdin    | Hereditary tyrosinemia type 1                                                | MDK-Nitisinone, Nitisinone                                                      |
| Nitisinone36              | Galafold    | Fabry disease                                                                | Fabrazyme                                                                       |
| Migalastat35              | Procsybi    | Nephropathic cystinosis                                                       | None                                                                             |
| Cysteamine bitartrate56   | Cerdelga    | Gaucher disease                                                              | None                                                                             |
| Eliglustat57              | Ocivia      | Primary biliary cholangitis                                                   | Cerezyme, Elelyso, Zavesca                                                     |
| Obeticholic acid38        | Ravici      | Urea cycle disorders                                                         | Ursodiol                                                                        |
| Glycerol phenylbutyrate29 | Uptravi     | Pulmonary arterial hypertension (WHO class II and III)                        | Volibris                                                                        |
| Selupig10                 | Kuvan       | Phenylketonuria                                                              | None                                                                             |
| Sapropterin dihydrochloride41 | Egrifta    | Lipodystrophy in HIV-infected patients                                        | None                                                                             |
| Tesamorelin42             | Revestive   | Short bowel syndrome                                                         | None                                                                             |
| Teduglutide43             | Ilaris      | Systemic juvenile idiopathic arthritis                                       | Aczemra                                                                        |
| Canakinumab44             | Vimizim     | Macropolyascharidosis IVA (Marquio A Syndrome)                               | None                                                                             |
| Elosiufase alfa45         | Humira      | Hidradenitis suppurativa                                                     | None                                                                             |
| Adalinumab46              | Pheburane   | Urea cycle disorders                                                         | None                                                                             |
| Sodium phenylbutyrate47   | Strensiq    | Hypophosphatasia pediatric onset                                             | None                                                                             |
| Asfotase alfa48           | Jinarc      | Autosomal dominant polycystic kidney disease                                 | None                                                                             |
| Tolvaptan49               | Elelyso     | Gaucher disease                                                              | Cerezyme, Cerdelga, Zavesca                                                     |
| Taliglucerase alfa50      | Jinarc      | Autosomal dominant polycystic kidney disease                                 | Cerezyme, Repatha                                                              |
| Lomiptapide51             | Juxtapid    | Familial Homozygous Hypercholesterolemia                                     | None                                                                             |
| Abobotulinum toxin52      | Dysport Therapeutic | Cervical dystonia                             | Flolan, Volibris, Ambriasantan, Remodelin, Tracleer, Uptravi, Opsumit, Ambriasantan |
| Macitentan53              | Opsumit     | Pulmonary arterial hypertension                                               | None                                                                             |
| Riociguat54               | Adempas     | Pulmonary arterial hypertension (WHO class I)                                | None                                                                             |

(aborotulinum toxin A, macitentan, and riociguat) presented data from a cost-minimization analysis (CMA), with one of them also presenting an indirect treatment comparison, although these analyses had some uncertainties according to CADTH CDR, all of these drugs were approved with recommended price reductions.

Treatment Alternatives
In this review, we noticed that 15 of the orphan drugs included, did not have any treatment alternatives for the condition they are indicated for, and hence can be categorized as Therapeutic Criteria Level I according to the new PMPRB guidelines. For the medicines categorized as Therapeutic Criteria Level I, except for toclizumab none of the other medicines have met CAD $200,000 per QALY threshold set by PMPRB for the base-case. Of the other medicines that are not categorized as Therapeutic Criteria Level I, included in the review, only two other drugs (nitisinone, obeticholic acid) have met the CAD $150,000 per QALY threshold.

Price Reduction Recommendations
In order to approve the drugs for reimbursement, CADTH generally used CAD $50,000 per QALY and CAD $100,000 per QALY to recommend price reductions for the drugs, when the drugs did not meet the threshold at manufacturer set price (See Table 2 for price
| Drug | Brand Name | Comparator Model | Manufacturer Base Case ICUR | CET Threshold with Price Reduction Conditions | Treatment Recommended | Price Reduction Conditions |
|------|------------|------------------|-----------------------------|-----------------------------------------------|----------------------|-----------------------------|
| Barasartan<sup>30</sup> | Cryopia | Markov model with 3 health states for pediatric and adult patients | $53,000 per QALY | $1.97 million per QALY in pediatric patients, $1.1 million per QALY in adult patients | Yes | 95% for pediatric patients, 94% for adults |
| Barasartan<sup>30</sup> | Vynabeg | Markov model with 3 health states | $53,000 per QALY | $1.97 million per QALY in pediatric patients, $1.1 million per QALY in adult patients | Yes | 95% for pediatric patients, 94% for adults |
| Bevacizumab<sup>45</sup> | Tocilizumab<sup>47</sup> | Markov model with 2 health states | $53,000 per QALY | $1.97 million per QALY in pediatric patients, $1.1 million per QALY in adult patients | Yes | 95% for pediatric patients, 94% for adults |
| Bevacizumab<sup>45</sup> | Talazoparib | Markov model with 1 health state | $53,000 per QALY | $1.97 million per QALY in pediatric patients, $1.1 million per QALY in adult patients | Yes | 95% for pediatric patients, 94% for adults |
| Bevacizumab<sup>45</sup> | Inotersen | Markov model with 1 health state | $53,000 per QALY | $1.97 million per QALY in pediatric patients, $1.1 million per QALY in adult patients | Yes | 95% for pediatric patients, 94% for adults |
| Bevacizumab<sup>45</sup> | Cystine | Markov model with 1 health state | $53,000 per QALY | $1.97 million per QALY in pediatric patients, $1.1 million per QALY in adult patients | Yes | 95% for pediatric patients, 94% for adults |
| Bevacizumab<sup>45</sup> | Spinraza | Markov model with 1 health state | $53,000 per QALY | $1.97 million per QALY in pediatric patients, $1.1 million per QALY in adult patients | Yes | 95% for pediatric patients, 94% for adults |
| Bevacizumab<sup>45</sup> | Nusinersen | Markov model with 1 health state | $53,000 per QALY | $1.97 million per QALY in pediatric patients, $1.1 million per QALY in adult patients | Yes | 95% for pediatric patients, 94% for adults |
| Bevacizumab<sup>45</sup> | Brineura | Markov model with 1 health state | $53,000 per QALY | $1.97 million per QALY in pediatric patients, $1.1 million per QALY in adult patients | Yes | 95% for pediatric patients, 94% for adults |
| Bevacizumab<sup>45</sup> | Spinraza | Markov model with 1 health state | $53,000 per QALY | $1.97 million per QALY in pediatric patients, $1.1 million per QALY in adult patients | Yes | 95% for pediatric patients, 94% for adults |
| Bevacizumab<sup>45</sup> | Nusinersen | Markov model with 1 health state | $53,000 per QALY | $1.97 million per QALY in pediatric patients, $1.1 million per QALY in adult patients | Yes | 95% for pediatric patients, 94% for adults |
| Bevacizumab<sup>45</sup> | Brineura | Markov model with 1 health state | $53,000 per QALY | $1.97 million per QALY in pediatric patients, $1.1 million per QALY in adult patients | Yes | 95% for pediatric patients, 94% for adults |

**Table 2** Cost–Utility Analyses of Drugs for Rare Diseases Assessed by CADTH CDR (January 2015-May 2020)
Table 2 (Continued).

| Drug | Brand Name | Comparator | Model | Time Horizon | Annual Drug Costs per Patient | Manufacturer Base Case ICUR | CADTH Revised Base Case ICUR | Price Reduction Conditions | CET Threshold with Price Reduction | Treatment Recommended |
|------|------------|------------|-------|--------------|--------------------------------|-----------------------------|-----------------------------|---------------------------|-----------------------------|---------------------|
| Sebelipase alfa<sup>63</sup> | Kanuma | BSC | Markov model in the infantile patients with 5 health states, and pediatric/adults with 9 health states | Lifetime | $892,000 to $4.9 million in infantile patients, $892,000 in pediatric/adult patients | $4,485,000 per QALY in infantile population, $2,005,000 per QALY in pediatric or adult population | $4.9 million per QALY and more than $2 million per QALY in infantile and pediatric/adult presentations. | 98% | $50,000 per QALY | Yes |
| Nitisinone<sup>64</sup> | Nitisinone | Dietary restriction | Markov model with 7 health states | 20 years | $34,626 for a 20kg patient, $130,343 for a 70 kg patient | $138,658 per QALY | $149,197 per QALY | 45% to 55% | Price matching | Yes |
| Nitisinone<sup>65</sup> | MDK-Nitisinone | Dietary restriction | Markov model with 3 health states in infants | 6 years | $18,998 for a 20kg patient, $179,124 for a 75 kg patient | $62,823 per QALY | Could not be determined | 60% | Price matching | Yes |
| Tocilizumab<sup>66</sup> | Actemra | Prednisone | Semi-Markov model with 5 states | Lifetime | $18,663 | $82,496 per QALY | $187,389 per QALY | 65% | $50,000 per QALY | Yes |
| Nitisinone<sup>67</sup> | Orfadin | Dietary restriction/ BSC | Semi-Markov cohort model with 3 states | Lifetime | $70,614 for a 20kg patient, $267,850 for a 75 kg patient | $320,985 per QALY | $377,025 per QALY | 74% | $100,000 per QALY | Yes |
| Migalastat<sup>68</sup> | Galafold | Blended ERTs | Markov model with 10 health states | 50 years | $310,250 | Dominant | Migalastat vs agalsidase alfa: $200,487 to $55.9M per QALY migalastat vs agalsidase alfa: dominant | Price matching or lower | Yes |
| Cysteamine bitartrate<sup>69</sup> | Procysbi | No treatment (complication management only) | Markov model with 7 health states | Lifetime | $136,000 to $321,000 | $675,605 per QALY | $1,124,329 per QALY | 95% | $100,000 per QALY | Yes |
| Drug                  | Comparative | Model          | Horizon | Cost                  | Effectiveness          | Price Matching | ICER Matched | ICER Unmatched |
|-----------------------|-------------|----------------|---------|-----------------------|------------------------|---------------|--------------|---------------|
| Eliglustat            | Cordelia    | Markov model   | Lifetime| $253,675 for poor metabolizers or $507,350 for intermediate and extensive metabolizers | Dominates both comparators |               |              |               |
|                       | Cerdelga    |                |         |                       | Treatment naïve patients: Eliglustat dominated by imiglucerase; ~ $1.3B/QALY vs velaglucerase. Treatment stable patients: Eliglustat is dominated by imiglucerase and velaglucerase |               |              |               |
| Obeticholic acid      | Ocaliva     | Markov model   | 50 years| $36,000               | UDCA-tolerant patients: $82,921 per QALY for OCA vs OCA plus UDCA vs UDCA alone UDCA intolerant patients: $6,1365 for OCA alone vs no treatment |               |              |               |
| Obeticholic acid      | Ocaliva     | UDCA-tolerant: oral UDCA UDCA intolerant: placebo (no treatment) |         |                       | Treatment naïve patients: Eliglustat dominated by imiglucerase; ~ $1.3B/QALY vs velaglucerase. Treatment stable patients: Eliglustat is dominated by imiglucerase and velaglucerase |               |              |               |
| Glycerol phenylbutyrate | Ravicti   | Markov model   | Up to 100 years | $4,565 (<2 years old) to $1,197,674 (≥18 years) | $718,620 to $6,284,096 per QALY |               |              |               |
| Selexipag             | Uptravi     | Patient-level Micro-simulation approach | Lifetime | $46,842               | $187,418 per QALY for selexipag + current therapy vs current therapy |               |              |               |
| Sapropterin dihydrochloride | Kuvan    | Markov model with annual cycle, with 5 health states | Lifetime | $12,000 to $169,000 | $274,862 to $308,664 per QALY |               |              |               |
| Tesamorelin           | Egrifta     | Decision tree  | Lifetime | $37,534               | $66,735 per QALY        |               |              |               |
| Teduglutide           | Revestive   | Markov model with 8 health states | 40 years | Not reported          | $1,600,145 per QALY       |               |              |               |
| Drug       | Brand Name | Comparator        | Model                          | Time Horizon | Annual Drug Costs per Patient | Manufacturer Base Case ICUR | CADTH Revised Base Case ICUR | Price Reduction Conditions | CET Threshold with Price Reduction | Treatment Recommended |
|------------|------------|-------------------|--------------------------------|--------------|--------------------------------|----------------------------|----------------------------|-------------------------------|--------------------------------|--------------------------|
| Canakinumab | Ilaris     | First line: tocilizumab intravenous (IV) infusion Second line: BSC | Micro-simulation model | Up to 18 years (patients remain in the model up to age 20). | $208,000 to $416,000 | First line: $3,273,360 to $1,036,258 per QALY. Second line: $824,830 to $307,981 per QALY. | First line: $1,846,134 to $6,521,275 per QALY Second line: $459,068 to $1,584,896 per QALY. | 79% to 94% | $100,000 per QALY | Yes |
| Biosulfase alfa | Vimizim | BSC | Markov model with 7 health states | Lifetime | Not reported | $1,720,127 per QALY. | $3.18 million per QALY | 97% | $100,000 per QALY | Yes |
| Adalimumab  | Humira     | BSC alone         | Markov model with 5 health states | 10 years | $39,979 in the first year and $38,499 thereafter | $62,794 per QALY | $377,516 per QALY | 90% | $40,297 per QALY | Yes |
| Asfotase alfa | Strensiq | BSC | Markov model with 6 health states | Lifetime | > 1 million per year for patients weighing >20kg | Did not report | $2,698,950 per QALY | 90% | Not enough for acceptable thresholds | Yes |
| Tolvaptan   | Jinarc     | BSC               | Markov model with 5 health states | Lifetime | Not reported | $244,402 per QALY | $387,000 per QALY | 73% | $50,000 per QALY | No |

**Abbreviations:** BSC, best supportive care; QALY, quality adjusted life year; SMA, spinal muscular atrophy.
reductions). In 12 of the drugs approved, a $50,000 per QALY threshold was used to recommend a price reduction in the range of 32% (glycerol phenylbutyrate) to 98% (patisiran). In another 7 drugs that were approved, a CAD$100,000 per QALY threshold was used to recommend a price reduction in the range of 74% (nitisinone (Orfadon)) to 99% (cerliponase alfa). Seven of the drugs approved were recommended to reduce the price to match drug plans of other treatments for the disease of interest. While for one drug (asfotase alfa), CADTH noted that even a 90% price reduction would not be sufficient to meet acceptable thresholds. Also, a CAD $400,000 per QALY threshold was used to recommend a price reduction for nusinersen, and even with a 95% price reduction, the drug was still not cost-effective. Another approved drug (migalastat) did not have any price reduction conditions for approval. All of the drugs that were not recommended by CADTH for reimbursement did not show improvements of clinical significance in the evidence submitted and CADTH also had some concerns about the long-term safety. It is unclear why CADTH CDR chose CAD$50,000 per QALY for some drugs and CAD$100,000 per QALY for the others to recommend price reductions.

**Patient Inputs**

Patient inputs were also considered by CADTH CDR for all the drugs included in this review. Overall, in 24 of the drugs included in this review, patients expressed an unmet need for the treatments, of which in 10 drugs the unmet need was arising from inconveniences such as intravenous infusions with current treatments. In another eight drugs included in this review, patients said that the drug under the review was the only treatment available. While in seven other drugs, patients felt that their condition improved after the treatment with the drug. Patient inputs from two drugs (inotersen, patisiran) said that the current treatments cannot stop disease progression, and there was an unmet need to find a treatment that can actually alter the course of the disease.

**Discussion**

Our review showed that none of the drugs included in this study met the WTP threshold of CAD$50,000 or CAD $100,000 per QALY used by CADTH CDR for their ICUR. Only one drug met the CAD$200,000 per QALY for Therapeutic Criteria Level I, and two other drugs met CAD$150,000 per QALY for other Therapeutic Criteria Levels proposed by PMPRB, with the CADTH CDR revised base case analyses. Orphan drugs included in this review were able to meet the ICUR thresholds only in the scenario where the price discounts suggested by CADTH CDR were applied. However, in spite of not meeting the acceptable thresholds with the manufacturer list price, the majority of drugs considered were later approved for reimbursement with price reduction recommendations to meet acceptable thresholds. The pan-Canadian Pharmaceutical Alliance (pCPA), an alliance of Canadian provinces, territories and some federally funded drug programs negotiates with manufacturers of both branded and generic drugs to achieve greater value for publicly funded drugs by obtaining discounts through “bulk buying”. Some of the orphan drugs approved for reimbursement in this review have also progressed through the negotiations with pCPA to be listed in provinces. Previous studies have shown that using standard HTA procedures, such as incremental cost per QALY, typically results in orphan drugs not being cost-effective, even when they have an exceptional efficacy profile.7,12–15 This begs the question on whether there is an overreliance on cost-effectiveness thresholds as the main basis for the evaluation of orphan drugs for reimbursement decisions and, even more concerning, as a basis for price setting. This question is all the more relevant when cost-effectiveness ratios are derived from economic models and data which themselves contain significant uncertainties.

Our review also showed that CADTH CDR considered unmet need and severity of the disease as important elements in the reimbursement decision-making. Although this review did not focus on patient and caregiver perspectives in the reimbursement process of orphan drug submissions to CADTH CDR, we noticed that patients and caregivers emphasized a lack of treatment alternatives for several drugs, inconveniences with current treatments such as intravenous infusions as a part of treatment, and adverse event experiences with current treatments. In a majority of the drugs reviewed, patient groups consulted for their inputs about the new treatments were hopeful of the new treatment. This study also showed that some of the drugs included did not have Health Canada approved treatment alternatives and that BSC was the only option for several conditions, considering patient inputs about lack of treatment alternatives, all emerging rare disease drugs without treatment alternatives should be viewed more favorably from a patient perspective by HTA agencies in order to address the health-care needs of patients with rare diseases.
Since rare diseases affect such few numbers of patients, paucity of evidence with respect to randomized controlled trials enrolling participants and having control groups, as well as epidemiological evidence from observational studies is to be expected. Lack of epidemiological evidence also means there will be limited data availability for the natural history of the disease and long-term effectiveness, and this might lead to imperfect data for health states in the economic models and uncertainty in the benefits and budget impacts of the drugs.\textsuperscript{7,16} Real-world evidence (RWE) generation, pay-for-performance and managed access agreements are among the reimbursement mechanisms available to patients, clinicians and payers.\textsuperscript{17} Canadian regulators and payors could use these mechanisms to support patients while developing a better understanding of the cost and value of rare disease treatments. While from a cost-per-patient or cost-per-QALY standpoint, orphan drugs seem to be expensive, overall, they will have limited impact on health-care budgets given the fewer numbers of patients requiring treatment.\textsuperscript{12,18} Also, previous research has shown that while orphan drugs appear to have higher incremental costs and are seemingly less cost-effective, they tend to offer larger health gains when compared to non-orphan drugs.\textsuperscript{19}

**Conclusion**

This review showed that no rare disease drugs submitted to CADTH over the past five years have met the arbitrary ICUR thresholds and using such thresholds make it challenging for rare disease drugs to appear cost-effective. Considering the difficulties for HTA agencies to interpret the results of an economic evaluation associated with a level of uncertainty inherent to orphan drugs, the proposed PMPRB guidelines and federal regulations will potentially lead to obstacles for manufacturers of rare disease treatments to meet Canadian pricing regulations. Manufacturers having to reduce the prices substantially (eg, up to 90% or more) to meet the new requirements might find the business model to be unsustainable and this may jeopardize the launch of some new medicines in Canada. Additionally, denying access to some orphan drugs based on the proposed guidelines might limit the opportunities to add to the development of RWE which can be used in reimbursement approaches such as pay-for-performance. Furthermore, for the new drugs that perform better over time and with the availability of additional evidence, the MRP should be adjusted more favorably to the manufacturer and price revisions should serve as an incentive to the manufacturers for future launches of new treatments into Canadian market.

**Disclosure**

CB, LG, ED, KY, and KD are employees of the Pharmalytics Group. SB and JL are employees of Alexion Pharmaceuticals. Chakrapani Balijepalli and Eric Druyts report being a shareholders of the Pharmalytics Group. Alexion Pharmaceuticals has provided the funding support for the publication of this article. The authors report no other potential conflicts of interest for this work.

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