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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

VORETIGENE NEPARVOVEC (LUXTURNA — NOVARTIS PHARMACEUTICALS CANADA INC.)
Indication: Vision loss, inherited retinal dystrophy

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that voretigene neparvovec be reimbursed for the treatment of patients with vision loss due to inherited retinal dystrophy (IRD) caused by biallelic retinal pigment epithelium 65 kDa protein (RPE65) mutations only if the following conditions are met:

Conditions for Reimbursement
Initiation criteria
1. Patients who have all of the following characteristics:
   1.1. Biallelic RPE65 mutations, as confirmed by an accredited laboratory using validated assay methods.
   1.2. Possess sufficient viable retinal cells, as determined by an inherited retinal disease specialist.
   1.3. At least four years of age.
   1.4. Visual acuity worse than 20/60 (both eyes) and/or visual field less than 20 degrees in any meridian as measured by III4e isopter or equivalent (both eyes).

Prescribing conditions
1. Treatment should be limited to one treatment per eye per patient lifetime.
2. Patient selection and the pre- and post-surgical evaluations should be carried out by a physician who specializes in inherited retinal diseases.
3. Treatment with voretigene neparvovec should be administered by a retinal surgeon experienced in performing submacular injection and management of associated complications.

Pricing conditions
1. Reduction in price.

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   - 1.1. biallelic RPE65 mutations, as confirmed by an accredited laboratory using validated assay methods.
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1. Treatment should be limited to one treatment per eye per patient lifetime.
2. Patient selection and the pre- and post-surgical evaluations should be carried out by a physician who specializes in inherited retinal diseases.
3. Treatment with voretigene neparvovec should be administered by a retinal surgeon experienced in performing submacular injection and management of associated complications.

Pricing conditions

1. Reduction in price.

Reasons for the Recommendation

1. One randomized, open-label, phase III trial (Study 301, N = 31) evaluated the efficacy and safety of sequential subretinal injections of voretigene neparvovec to each eye in patients diagnosed with leber congenital amaurosis (LCA) due to RPE65 mutations. Voretigene neparvovec demonstrated a statistically significant improvement in functional vision under low light conditions as measured by multi-luminance mobility testing (MLMT) at one year post-treatment compared with best supportive care (change from baseline in bilateral MLMT between-groups difference: 1.6 [95% CI, 0.72 to 2.41; P = 0.001]). This improvement in functional vision would likely be considered meaningful to patients. Voretigene neparvovec also resulted in a statistically significant improvement in full-field sensitivity threshold (FST) one year post-treatment (mean between-groups difference: −2.11 log units, 95% CI, [−3.19 to −1.04; < 0.001]).
2. CDEC acknowledged that there is an unmet need for a pharmaceutical and/or surgical treatment of vision loss due to IRD caused by confirmed biallelic RPE65 mutations and that voretigene neparvovec is the first treatment approved in Canada that targets the underlying mechanism of the disease.
3. Based on the CADTH reanalysis of the manufacturer-submitted economic model, voretigene neparvovec is associated with an incremental cost-effectiveness ratio (ICER) of $200,477 per quality-adjusted life-year (QALY) gained compared with best supportive care (BSC). However, this estimate is associated with significant uncertainty as the majority of the modelled benefits were accrued in time periods beyond when clinical data are available. Clinical estimates for natural history and treatment effectiveness were uncertain, and the model was sensitive to the assumed duration of treatment effects. Based on the CADTH reanalysis, a price reduction of more than 74% would be required to achieve ICERs below $50,000 per QALY.

Implementation Considerations

- Genetic testing required to confirm the presence of biallelic RPE65 mutations may not be available in all jurisdictions. CDEC suggested that given the uncertainty regarding the availability of these tests and the potential for such tests to place an additional financial burden on the public health care system, the sponsor should be required to ensure that these tests are available and financed to support the implementation of the reimbursement of voretigene neparvovec.
- Measuring viable retinal cells is not a straightforward procedure, and there is no benchmark or threshold of viable retinal cells that can be used to objectively define the sufficient viable retinal cells criterion. Given the variability and subjectivity inherent in determining the sufficiency of viable retinal cells, CDEC recommends that the presence of sufficient viable retinal cells be confirmed by more than one inherited retinal disease specialist, where feasible. CDEC recognized that because some jurisdictions might not have access to a sufficient number of specialists to implement this recommendation, public drug plans should consider whether a pan-Canadian approach would be feasible, such as leveraging clinical expertise in larger jurisdictions through the establishment of a centralized panel or committee of retinal specialists that could assess the sufficiency of retinal cell viability.
- The economic analysis was associated with substantial uncertainty regarding the cost-effectiveness of voretigene neparvovec, due largely to the uncertainty associated with the long-term efficacy of the treatment. This was reflected in the observation that the pharmacoeconomic results were extremely sensitive to assumptions about the expected duration of the treatment effect with voretigene neparvovec. Given the extent of uncertainty regarding the cost-effectiveness of this product and the extremely high cost of treatment, jurisdictions may wish to consider establishing product listing agreements that mitigate the long-term financial risk to public payers.

Discussion Points

- CDEC discussed the potential that younger patients might exhibit a better response to treatment than adult patients, likely due to more extensive structural damage typically observed in adults with IRDs; however, the clinical experts consulted by CADTH felt that age was not an appropriate criterion for determining whether patients were suitable for treatment with voretigene neparvovec, but rather the presence of sufficient viable retinal cells.
- CDEC discussed that there is no benchmark or threshold of viable retinal cells that can be used to objectively define the sufficient viable retinal cells criterion. The clinical experts consulted by CADTH indicated that a numerical cut-off could not be applied universally throughout all optical coherence tomography (OCT) technologies and generations. In clinical practice, the presence of sufficient viable retinal cells would be determined by the treating physician using OCT examinations, measuring the area of remaining viable photoreceptors, which would be supplemented by visual acuity and visual function tests. Given that there is no universally accepted definition of sufficient viable retinal cells, CDEC discussed that the expert opinion of at least two inherited retinal disease specialists be sought to confirm the presence of sufficient viable retinal cells.
- CDEC discussed that there is uncertainty regarding whether the observed magnitude of difference in MLMT score between voretigene neparvovec and the control group in Study 301 can be considered clinically meaningful. The sponsor indicated that an average change of one-light level was considered clinically significant. However, the European Medicines Agency indicated that any clinically relevant change in MLMT with voretigene neparvovec would need to exceed one-light level, and the FDA indicated that a clinically meaningful change in MLMT score was two or greater. CDEC also discussed that scores on the MLMT may underestimate the treatment effect of voretigene neparvovec due to the potential ceiling effect where patients who passed the test at the second lowest light level at baseline were only able to achieve a maximum 1-unit increase.
- There is uncertainty associated with the duration of the treatment effect of voretigene neparvovec. The clinical experts consulted by CADTH indicated that it is expected that treatment response will wane over time. Improvements observed with voretigene neparvovec after one year appeared to be maintained up to four years; however, these data were limited by the open-label trial design, the lack of a comparator and statistical analysis one year after randomization.
- CDEC discussed that some jurisdictions might not have access to genetic testing and genetic counselling. This should be considered in light of the condition that requires molecular diagnosis and the uncertainty regarding the availability of these tests in Canadian jurisdictions.
- CDEC discussed that although the benefit-risk profile appears to be acceptable, some patients may experience serious adverse events (SAEs) associated with the administration procedure of voretigene neparvovec.

- Given the progressive nature of IRD which leads to permanent vision loss and frequent onset of symptoms in childhood, the lack of other treatment options, the rarity of the condition, and the potential societal benefits of voretigene neparvovec treatment, CDEC discussed whether these aspects may require additional consideration by individual jurisdictions when making reimbursement and implementation decisions. However, CDEC also discussed that this should be further considered in light of the high degree of uncertainty regarding the long-term efficacy of voretigene neparvovec.

Background

Voretigene neparvovec has a Health Canada indication for the treatment of adult and pediatric patients with vision loss due to IRD caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells. Voretigene neparvovec is a vector-based gene therapy designed to deliver a normal copy of the gene encoding the human RPE65 to cells of the retina in persons with reduced or absent levels of biologically active RPE65. It is available as vector genomes/mL concentrate for solution for subretinal injection and the Health Canada–approved dose is 1.5 x 10^{11} vector genomes (vg) for each eye.

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by CADTH: a systematic review that included a single randomized controlled trial (RCT) of voretigene neparvovec and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with IRD, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group submission was received for this review which was authored jointly by Fighting Blindness Canada (FBC), the Canadian Council of the Blind (CCB), the CNIB Foundation, and Vision Loss Rehabilitation Canada. The submission was mainly oriented around a survey (N = 537); the analysis was done by FBC and the submission was developed collaboratively by all of the submitting organizations. The following is a summary of key input from the perspective of the patient groups:

- Patients indicated that their eyesight has some degree of interference with most daily activities, including mobility and getting around, hobbies/leisure, socializing and interacting with others, looking after their appearance, reading a book or a newspaper, and using phone or tablet.
- Patients worry about their condition getting worse, struggle with challenges presented by daily activities including parenting, experience long wait times for appointments, feel anxiety and uncertainty about the future and the impact of their diseases on their families, and in some cases experience a negative impact of a lack of meaningful work, education, or social life.
- No pharmacologic or surgical treatments were described in the patient group submission. However, a wide variety of modifications or aids such as canes, magnifiers, and specialized laptops are available to patients for daily activities.
- Patients expressed a desire for cure of the condition entirely, improved night vision and mobility at night, or improvements in regular day-to-day activities such as social interactions, maintaining personal relationships, work, and study. Most surveyed indicated that even if the treatments were only to enhance vision and mobility at night, their overall quality of life would be improved. Many respondents also indicated that a treatment that would at least halt the progression of vision loss would be valuable.

Clinical Trials

The systematic review conducted by CADTH included one study (Study 301). Study 301 (N = 31) was a phase III, open-label, RCT, designed to evaluate the efficacy and safety of sequential subretinal injection of voretigene neparvovec to each eye in patients diagnosed with LCA due to RPE65 mutations. Randomization occurred in a two-to-one ratio of intervention (voretigene neparvovec) to control and used a block design stratified by age (> 10 years versus < 10 years) and mobility testing passing level (pass at > 125 lux versus < 125 lux) as determined at screening. A total of 31 patients in two study sites in the US (the study enrolled international patients, including one patient from Canada) were randomized to either the voretigene neparvovec group (n = 21) or the control group (n = 10). Patients randomized to the voretigene neparvovec group received a dose of 1.5 x 10^{11} vg of voretigene neparvovec in each eye; the non- simultaneous, subretinal injections occurred within an eighteen-day period (twelve days ± 6 days). Patients

randomized to the control group did not receive voretigene neparvovec, sham injection, or corticosteroids for a period of at least one year from baseline evaluations. Following repeated retinal and visual function analysis, including mobility testing, at one month, three months, six months, and one year, patients in the control group were crossed over to receive non-simultaneous injections of 1.5 x 10^{11} vg of voretigene neparvovec to each eye (within eighteen days) after one year of randomization, provided they still met all study eligibility criteria. Two patients were prematurely withdrawn from the study: one patient was randomized to the voretigene neparvovec group but was withdrawn by the investigator before receiving the study drug, and one patient was randomized to the control group but was discontinued early due to withdrawn consent. All other patients completed the study through year 1.

Key limitations of Study 301 were the open-label design of the study and imbalances in the baseline patient characteristics between the voretigene neparvovec and control groups, which included age and visual performance. Scores on the MLMT may underestimate the treatment effect of voretigene neparvovec due to the potential ceiling effect where patients who passed the test at the second lowest light level at baseline were only able to achieve a maximum 1-unit increase. Further, the MLMT was developed by the sponsor and there is some uncertainty over the accepted definition of a clinically relevant improvement.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, CDEC discussed functional vision, visual function, and the visual function questionnaire.

- Functional vision
    - MLMT — The MLMT quantifies a patient's ability to navigate an obstacle course under varying environmental illuminations, including very low light levels. A person with 20/20 vision would complete the course at 1 lux with no or minimal errors, which corresponds to the level of light available on a moonless summer night or from an indoor night light. At the other end of the scale would be a light level of 400 lux, which equates to the level of light available within a well-illuminated indoor setting. Passing the MLMT at any light level is defined as completing the course at the specified light level with fewer than four errors and within three minutes. The test had 12 course configurations to reduce the learning effect. Patients were evaluated for accuracy and speed on the MLMT at 7 standardized light levels (1, 4, 10, 50, 125, 250, and 400 lux). Each light level was assigned a discrete lux score from −1 to 6, with lower light levels corresponding to higher lux scores (i.e., -1 score was assigned for more than 400 lux and a score of 6 was assigned for 1 lux). Baseline testing was used to establish the lowest level of illumination at which each patient could pass the MLMT, with the change score defined as the difference in lux scores relative to baseline. A positive change score indicates passing the MLMT at a lower light level. The sponsor indicated that an average change of one-light level in passing the MLMT was considered clinically significant. However, the US FDA indicated that an MLMT score change of one may represent a background fluctuation occurring in both the treatment and the control groups, and that the clinically meaningful MLMT score change considered was two or greater.
- Visual function
    - FST— The FST is a measure of light sensitivity of the entire visual field and is aimed at detecting the lowest luminance of a flash detected by a patient. In this test, flashes of various luminance (range spanning approximately 80 decibels [dB]) are presented to individuals, who are then asked to press a response button if they are able to see the visual stimulus. FST results are expressed in dB, which are then converted to log10 (cd.s/m2) to accommodate different dB conversion rates. Smaller values of dB and cd.s/m2 indicate better sensitivity, and negative log10 (cd.s/m2) values indicate better sensitivity. No evidence was found in the literature for the validity and responsiveness of patients diagnosed with IRD or other conditions. The sponsor reported a minimal important difference (MID) of 10 dB or 1 log change for the FST test.
    - Visual acuity (VA) — VA is a measure of the ability of the eye to distinguish shapes and the details of objects, also knowns as optotypes, (individual letters of standardized size and contrast presented to the test taker for VA assessment) from a set viewing distance. In Study 301, the VA was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart. Scoring for ETDRS charts is designed to produce a logarithmic minimal angle of resolution score (LogMAR) suitable for statistical analysis in which individual letters score 0.02 log units. Information submitted by the sponsor indicated that a 0.1 improvement in LogMAR corresponded to a five-letter improvement (or the equivalent of one line) on an ETDRS eye chart. Notably, a decrease in LogMAR score represents an improvement in VA. Among patients in Study 301 who were unsuccessful in correctly identifying the largest line of letters in the ETDRS chart, off-chart VA measurements were collected by counting fingers, and

evaluating hand motion perception, light perception, and no light perception. For off-chart VA measurements, LogMAR values were assigned using the scale adapted from Holladay et al. An IRD-specific MID for ETDRS was not identified from the literature. A study based on patients with macular edema estimated that a meaningful change in ETDRS is typically defined as greater than three lines (15 letters, equivalent to 0.3 LogMAR). An improvement of LogMAR 0.3 (i.e., ≤ − LogMAR 0.3) was considered clinically meaningful by the FDA medical review of voretigene neparvovec.

- Visual function questionnaire
    - Visual function questionnaire-25 (VFQ-25) — The VFQ-25 is a 25-item version of the original 51-item National Eye Institute Visual Function Questionnaire (VFQ) that is available in both self-administered format and interviewer-administered format. This patient-reported survey measures the effect of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning, in addition to activities of daily living. The VFQ used in Study 301 was modified by the investigative team to evaluate the activities of daily living that are dependent on vision, or have a vision element, with items related to health-related quality of life (HRQoL) removed. The adaptations were made to accommodate IRD-associated poor vision and to include a pediatric population. The scoring system was changed too, with the perceived difficulty of these activities rated on a 0 to 10 numerical scale (0 being the most difficult), before the average of the responses is taken to determine the numerical score for each individual. The adapted version of the VFQ used in Study 301 was not assessed psychometrically. An MID was neither assessed for the adapted version of the scale, nor was any evidence found based on the literature search. Given the modifications made to the original VFQ, the MIDs identified in the literature for that measure were not considered directly generalizable to the version used in Study 301.

The primary end point in Study 301 was change in MLMT performance at year 1 relative to baseline. Secondary end points were change in FST at year 1 relative to baseline, change in assigned first eye MLMT performance at year 1 relative to baseline, and change in VA averaged over both eyes relative to baseline.

Efficacy

The mean (SD) bilateral MLMT change score after one year was 1.8 (1.1) for the voretigene neparvovec group and 0.2 (1.0) for the control group. The difference in change from baseline in bilateral MLMT between voretigene neparvovec and control treatment groups at 1 year was 1.6 (95% CI, 0.72 to 2.41; P = 0.001), which was statistically significant in favour of voretigene neparvovec; however, the difference between the treatment groups did not exceed 2 points. Eleven patients (52%) in the voretigene neparvovec group had an MLMT score change of 2 or more (the difference considered meaningful by the FDA). In contrast, only one patient (10%) of the control group had a score change of 2, and none of the patients in the control group had a score change greater than 2. While 62% of patients in the voretigene neparvovec group achieved a score of 6 on the MLMT (the maximum possible score in MLMT) following administration of voretigene neparvovec, none of the patients in the control group achieved a score of 6 on the MLMT. The observed mean increase in MLMT score of 1.8 observed in the voretigene neparvovec group could be an underestimate of the within groups magnitude of the change due to the potential ceiling effect. Improvements in the MLMT score observed at one year seemed to be maintained until four-years follow-up.

Patients treated with voretigene neparvovec experienced a mean improvement in FST > 2 log units; whereas, mean FST did not change in the control group (mean [SE] change from baseline to year 1 of −2.08 [0.29] log10 (cd.s/m^2) for the voretigene neparvovec group and 0.04 [0.44] log10(cd.s/m^2) for the control group). There were statistically significant improvements in full-field light sensitivity with voretigene neparvovec (mean difference versus control −2.11 log units; 95% CI, −3.19 to −1.04; < 0.001) at 1 year. This between-group difference exceeded the sponsor's defined threshold of 10 dB or 1 log unit for clinical significance. The improvements were sustained for four years after the second eye injection, where for all patients who received treatment with voretigene neparvovec, the mean change from injection baseline at four years after the second eye injection was (−2.00 [1.35] log10 (cd.s/m^2)). The clinical experts consulted by CADTH explained that the changes seen would be clinically meaningful in terms of improving visual function.

The mean (SE) change from baseline to one year in VA using the Holladay scale was −0.16 (0.07) LogMAR for the voretigene neparvovec group and 0.01 (0.10) LogMAR for the control group, resulting in a mean treatment-effect difference of −0.16 LogMAR (95% CI, −0.41 to 0.08; P = 0.17) (an eight letter improvement). This difference was neither statistically significant nor clinically

meaningful. The clinical experts consulted by CADTH also noted that even if there were no improvement, preventing vision from deteriorating would be important for the patient's quality of life.

For the patient completed surveys of the VFQ, the mean (SD) change from baseline to year 1 was 2.6 (1.8) for the voretigene neparvovec group and 0.1 (1.4) for the control group, for a mean between-group treatment difference 2.4 (95% CI, 1.0 to 3.8; nominal P = 0.001). For the parent completed surveys, the mean (SD) change from baseline to year 1 was 3.9 (1.9) for the voretigene neparvovec group and −0.2 (1.3) for the control group, for a mean between-group treatment difference 4.0 (95% CI, 2.1 to 6.0; nominal P = 0.002). Although the VFQ assessed the ability to perform activities of daily living in patients who receive voretigene neparvovec, the questionnaire did not contain any items to specifically assess HRQoL for patients. In addition, the VFQ used in Study 301 was not assessed psychometrically, and given the modifications made to the original VFQ, the MIDs identified in the literature for that measure were not considered directly generalizable to the version used in Study 301.

Harms (Safety)

All patients in Study 301 experienced at least one treatment-emergent adverse event (TEAE). Most adverse events were mild in severity and no patient had adverse events that led to study discontinuation or death.

The most frequently reported TEAEs in the voretigene neparvovec group were leukocytosis in 45% of patients, vomiting in 40% of patients, nasopharyngitis, headache, and pyrexia in 35% of patients for each, oropharyngeal pain, cough, and nausea in 30% of patients for each, intraocular pressure increased in 20% of patients, cataract and hematuria in 15% of patients for each.

Overall, 13 (65%) patients in the voretigene neparvovec group had at least one TEAE considered to be related to the study drug administration procedure. The TEAEs most often considered to be probably related to the administration procedure were cataract and intraocular pressure increased (n = 3 [15%] patients for each).

During the control period, two (10%) patients in the voretigene neparvovec group experienced three SAEs at time points distant from vector administration. One patient experienced a possible seizure requiring hospitalization and one patient experienced an adverse drug reaction to medications administered during oral surgery requiring hospitalization.

At the time of the data cut-off for the Clinical Study Report of Study 301, which provided updated results of safety data through July 2, 2018, including follow-up for up to five years after the second injection for some patients, six SAEs occurred in five patients, including convulsion (one event), adverse drug reactions (two events) and retinal disorder (one event foveal thinning and loss of vision), retinal detachment (one event), pneumonia (one event), and menorrhagia (one event).

One ocular SAE occurred in Study 301, where a patient who received voretigene neparvovec experienced retinal disorder which was foveal thinning and loss of central vision and was related to the subretinal injection in this patient with pre-existing atrophy of the retina.

During the first year after the randomization period, in the voretigene neparvovec group, three patients experienced a cataract, two patients experienced retinal tear, and one patient developed an asymptomatic full thickness macular hole. During the follow-up, one patient who was originally in the control group and crossed over to voretigene neparvovec experienced retinal disorder which was foveal thinning and loss of central vision. Another patient experienced one SAE of retinal detachment.

Indirect Treatment Comparisons

No indirect evidence was submitted by the sponsor. An independent search conducted by CADTH did not find any published indirect evidence that met the inclusion criteria of the CADTH review protocol.

Cost and Cost-Effectiveness

At a submitted price of $515,750 per injection of voretigene neparvovec (one injection per eye), the one-time cost is $1,031,500 per patient assuming treatment in both eyes.

The sponsor submitted a cost-utility analysis comparing voretigene neparvovec to BSC (defined as low vision aids and supportive services related to medical vision care) for the treatment of vision loss in patients with RPE65-mediated IRD who have sufficient viable retinal cells. The analysis was conducted from the perspective of a Canadian publicly funded health care system adopting a lifetime time horizon. A Markov model captured health states based on vision health, as well as mortality. The patient cohort with RPE65-mediated IRD entered the model in different vision-related health states as per Study 301. Following the initial phase (one year in duration), individuals' vision may improve, remain the same, or decline. Following the initial phase, individuals treated with voretigene neparvovec entered a 40-year stabilization phase during which vision did not decline; whereas, individuals treated with BSC, or who received voretigene neparvovec after the stabilization phase, entered the long-term phase where vision could decline. Patients could transition from any health state to the absorbing death state. For the initial phase, transition probabilities in both the voretigene neparvovec and BSC arms were informed by the outcomes reported at one-year follow-up for Study 301. Disease progression in the long-term phase was informed by data from the RPE65 NHx study, a sponsor's commissioned retrospective chart review in which the natural history data were fitted to parametric multistate models (MSM). Health-state utilities were sourced from a sponsor-commissioned utility study in which six retina specialists assessed a series of health-state vignettes and assigned an impact on HRQoL using the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L). In the sponsor's base case, the ICER for voretigene neparvovec was $103,075 per QALY compared to BSC.

CADTH identified several key limitations with the submitted analysis:

- There is limited evidence on the duration of treatment effect. The manufacturer assumed 40 years which clinical experts consulted by CADTH considered it to be highly optimistic.
- RPE65 NHx had a high proportion of missing observations (approximately 80%) with data imputed based on last observation carried forward. This is inappropriate due to the progressive nature of the condition. Disease progression was described by fitting a parametric MSM that enforced progression by removing any contradictory data (i.e., improvements over time); this underestimated chance and measurement errors.
- Comparative treatment effects were informed by Study 301 which had a small sample size with imbalanced baseline characteristics. This introduced a high-risk of bias and resulted in less robust estimates.
- Health utilities used in the model were elicited from a small number of clinicians consulted by the sponsor rather than the general population or the patient population studied in the pivotal trials. Previous studies in different clinical settings have shown that valuation of health states by proxies typically underestimate the utility weight in chronic disability health states.
- Time dependency in the fitted multistate model was unlikely aligned with the time dependency in the long-term natural history of patients within the Markov model.

In the CADTH reanalysis, the duration of the treatment effect was set at 10 years; the crossover arm of Study 301 was used to inform the transition probabilities during the initial phase; and utility values were revised to include additional insights from the clinical experts consulted by CADTH. In the CADTH base case, the ICER of voretigene neparvovec was $200,477 per additional QALY compared to BSC. To achieve an ICER of $50,000 per QALY compared to BSC, the price of voretigene neparvovec would need to be reduced by more than 74%.

The submitted price of voretigene neparvovec is one of the key drivers of overall costs and ICERs. While the cost of voretigene neparvovec is known and incurred at the beginning of the model time horizon, the majority (96%) of the clinical benefit occurred outside the observed trial period (Study 301). Extrapolation of treatment effectiveness and natural history were associated with both significant parameter and structural uncertainties, where several assumptions could not be tested. The expected duration of treatment effect of voretigene neparvovec and the utility estimates were also key drivers in the model as noted from the additional scenario analyses conducted by CADTH. Together, these limitations indicate that the cost-effectiveness results should be cautiously interpreted.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

September 16, 2020 Meeting

Regrets

None

Conflicts of Interest

None