CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Glycopyrrolate (Cuvposa)

(Medexus Pharmaceuticals, Inc.)

Indication: Chronic severe drooling, neurologic (pediatric).

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Abbreviations

AE	adverse event
CDR	CADTH Common Drug Review
CP	cerebral palsy
CUA	cost-utility analysis
ICUR	incremental cost-utility ratio
GMFCS	Gross Motor Function Classification System
mTDS	modified Teacher's Drooling Scale
NICE	National Institute for Health and Care Excellence
QALY	quality-adjusted life-year
WTP	willingness to pay

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Glycopyrrolate (Cuvposa)
Study question	From the perspective of the publicly funded health care payer in Canada, what is the incremental cost-effectiveness of glycopyrrolate compared to no treatment for the treatment of chronic severe drooling in children with neurologic conditions (e.g., CP)?
Type of economic evaluation	Cost-utility analysis
Target population	Patients 3 to 18 years of age with neurologic conditions associated with chronic severe drooling
Treatment	Glycopyrrolate up to 0.1 mg/kg three times daily
Outcome	QALYs
Comparator	No treatment, informed in the base case by the placebo arm of the randomized clinical trial
Perspective	Canadian publicly funded health care payer
Time horizon	24 weeks
Results for base case	ICUR = $357,769 per QALY gained compared to no treatment
Key limitations	CADTH identified several key limitations with the submitted analysis: • Active comparators such as botulinum toxins were not considered. • The model was overly simplistic, including only a single transition point for treatment response without possibility of further improvement, loss of response, or treatment discontinuation. • The time horizon was insufficient to adequately assess all costs, harms, and benefits associated with treatment for a chronic condition. • The time point at which patients began to experience benefits from glycopyrrolate within the model was not consistent with the time point at which it was measured within the Zeller et al. clinical trial. • The sponsor assumed a disutility of 0.025 for each point of the mTDS score. This value was arbitrary in nature and was based on 5% of the utility assigned to the least severe state (0.5). • Baseline mTDS score differed between patients receiving glycopyrrolate and no treatment, suggesting possible differences in the two patient groups, which affects the ability to make a fair comparison and does not adequately model the introduction of glycopyrrolate into a single population. • The modelled age distribution was not consistent with the Zeller et al. trial, and patient weight was overestimated for the population modelled. • Adverse events were inappropriately excluded from the model.

CADTH estimate(s)	• The CADTH base-case reanalysis assessed efficacy at a time point consistent with the clinical trial (four weeks); pooled the baseline mTDS score which was applied to both the glycopyrrolate and no treatment groups; adjusted the patients' age distribution to be consistent with that found in the Zeller et al. trial; and assumed the patients' weights to be at the 25th percentile of Canadian growth charts. • CADTH's base case resulted in an ICUR of $292,274 per QALY. In order to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY, the submitted price of glycopyrrolate would need to be reduced by 83%. • These results are highly uncertain due to the number of limitations which could not be addressed in reanalysis, including: the oversimplification of the condition and treatment response, the lack of consideration of treatment discontinuation, the arbitrary nature of the health utility values assigned to an unvalidated efficacy outcome, and the exclusion of the impact of adverse events associated with glycopyrrolate from consideration within the model. • The cost-effectiveness of glycopyrrolate relative to active comparators currently used in Canada is unknown, as is its cost-effectiveness over a time horizon longer than 24 weeks.

CP = cerebral palsy; ICUR = incremental cost-utility ratio; mTDS = modified Teacher's Drooling Scale; QALY = quality-adjusted life-year.

Drug	Glycopyrrolate (Cuvposa)
Indication	To reduce chronic severe drooling in patients aged 3 to 18 years with neurologic conditions associated with problem drooling (e.g., cerebral palsy)
Reimbursement request	As per indication
Dosage form(s)	Oral solution
NOC date	October 30, 2017
Sponsor	Medexus Pharmaceuticals, Inc.

Executive Summary

Background

Glycopyrrolate oral solution (Cuvposa) is an anticholinergic drug indicated to reduce chronic severe drooling in patients three to 18 years of age with neurologic conditions (e.g., cerebral palsy [CP]).[1] It is available in a 1 mg/5 mL concentration in 473 mL bottles at a submitted price of $625.00 per bottle, or $6.61 per mL.[2] The recommended starting dose of glycopyrrolate is 0.02 mg/kg three times daily, titrated in increments of 0.02 mg/kg every five to seven days based on therapeutic response and adverse reactions. The maximum recommended dose is 0.1 mg/kg three times daily, not to exceed 1.5 to 3 mg per dose (see Table 11 for further details). For a 30 kg patient, depending on dose, the daily cost of glycopyrrolate at the submitted price may range from $11.98 to $59.46 (see Table 5).

The sponsor submitted a cost-utility analysis comparing glycopyrrolate oral solution to no treatment in the indicated population from the perspective of a Canadian publicly funded health care system over a 24-week time horizon.[2] The model structure was a decision tree in which patients in each group entered the model according to their baseline distribution on the modified Teacher's Drooling Scale (mTDS) scores as observed in Study FH-00-01, an eight-week, placebo-controlled randomized controlled trial (herein referred to as the Zeller trial).[3] The model allowed for a single transition in mTDS score at two weeks, which was based on the mTDS score distribution observed in the clinical trial at eight weeks.[3] Utility values were based on mTDS score and were taken from a 2017 National Institute for Health and Care Excellence (NICE) guideline,[4] where the utility of CP without drooling (mTDS score = 1) was assigned a value of 0.500, and each one-point increase in mTDS score was assigned a disutility of 0.025 (see Table 10). As the model allowed for transition only at week 2, utility weights were applied to the baseline mTDS score distribution for two weeks and to the post-treatment mTDS score distribution for weeks 3 through 24. Adverse events (AEs) were not considered. Only drug acquisition costs were included in the model, with dosage based on body weight. Patient age was sampled from a uniform distribution in the indicated age range of three to 18 years, and patients were assumed to have weights consistent with the 50th percentile from WHO growth charts for Canada.[5,6]

In their base case, the sponsor found that glycopyrrolate was associated with an incremental cost-utility ratio (ICUR) of $357,769 per quality-adjusted life-year (QALY) gained compared to no treatment.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified a number of limitations in the model submitted by the sponsor. Active comparators such as botulinum toxins and anticholinergics were not considered and the potential cost-effectiveness of glycopyrrolate against these comparators is unknown.

The model was overly simplistic, with only a single transition point for treatment response (week 2), and no possibility of further improvement, loss of response, or treatment discontinuation. Treatment response was captured within the model by the change in mTDS score, which is an unvalidated scale and thus increases uncertainty in the reliability and applicability of results. The time horizon was insufficient to adequately assess all costs, harms, and benefits associated with treatment for a chronic condition. The cost-effectiveness of glycopyrrolate beyond 24 weeks remains unknown, thus the true cost-effectiveness of glycopyrrolate is unknown.

In terms of efficacy, the transition point at which benefits began to be accrued within the model (after two weeks of treatment) was not consistent with the time point at which it was measured in the Zeller trial (after eight weeks of treatment). The disutility applied to each unit increase in mTDS score was arbitrary in nature, based on an assumption of 5% of the utility value for the least severe mTDS score (0.5 for mTDS = 1). The baseline population within the model was different between treatment groups, and this is not consistent with the decision problem which evaluates the potential cost-effectiveness of an intervention against its comparator within an identical population. Further, the modelled age distribution was not consistent with the clinical trial, and according to the clinical expert consulted by CADTH, the assumption regarding patient weight likely overestimated the weight of the indicated population.

Additionally, AEs were inappropriately excluded from the model, given that more patients in the glycopyrrolate group experienced treatment-emergent AEs, including severe gastrointestinal adverse events,[7] which could impact both cost and quality of life. Lastly, most parameters in the probabilistic analysis were based on a distribution with arbitrary variation and, therefore, the results may not reflect the true uncertainty associated with the model input parameters.

CADTH attempted to address some of these limitations, including assessing efficacy and the mTDS score distribution consistent with a common time point of measurement (four weeks) by combining the baseline mTDS scores from the trial population into a single pooled distribution to ensure an identical population was being compared within the model; altering the age distribution to be more consistent with the clinical trial that informed the efficacy estimates; and lowering the estimated weight of patients in the indicated population to the 25th percentile of Canadian growth charts. In CADTH's base case, glycopyrrolate is associated with 0.013 additional QALYs when compared to no treatment, at an additional cost of $3,884, for an ICUR of $292,274 per QALY compared to no treatment. To be cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY, the price of glycopyrrolate would need to be reduced by 83%.

Conclusions

After attempting to address several limitations with the sponsor's analysis, where possible, CADTH's base-case ICUR for glycopyrrolate compared with no treatment was $292,274 per QALY; a price reduction of 83% would be required in order for glycopyrrolate to be considered cost-effective at a WTP of $50,000 per QALY.

However, a number of larger issues remain which could not be addressed in the reanalysis, including the oversimplification of the condition and treatment response, the lack of consideration of treatment discontinuation, the lack of comparison to current standard of care or any active comparator, the arbitrary nature of the health utility values assigned to an unvalidated efficacy outcome, and the exclusion of AEs associated with glycopyrrolate from consideration within the model. Additionally, the effects of glycopyrrolate beyond 24 weeks are uncertain and no estimate of cost-effectiveness over a longer time period is possible. As such, the true cost-effectiveness of glycopyrrolate remains unknown.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a decision tree model comparing glycopyrrolate oral solution to no treatment for the treatment of chronic drooling in children with neurologic conditions (e.g., CP) from the perspective of a Canadian publicly funded health care system. No discounting of costs or outcomes (i.e., QALYs) was applied as the model was conducted over a time horizon of 24 weeks. Patients in each group entered the model in a distribution based on mTDS scores that were consistent with group-specific baseline scores observed in the Zeller trial, an eight-week, placebo-controlled randomized controlled trial .[3] The mTDS is a nine-point scale ranging from 1 (dry, never drools) to 9 (profuse drooling). The model allowed for a single transition in mTDS score at two weeks, which was based on the mTDS score distribution observed in the clinical trial's efficacy assessment at eight weeks.[3] No further improvement or deterioration in mTDS score was possible after this transition, and the no treatment group in the economic model was informed by the efficacy data from the placebo group of the trial.

Utility values were based on the mTDS score and taken from a 2017 NICE guideline on CP in patients under 25 years of age.[4] In this guideline, the utility of CP without drooling was assigned a value of 0.500, which was applied in the sponsor's model to patients in the indicated population with an mTDS score of 1. Thereafter, as assumed in the NICE guideline, each point of increase in mTDS score was assigned a linear disutility of 0.025, meaning patients with an mTDS score of 9 were assigned a utility weight of 0.300 (see Table 10). As the model allowed for transition only at week 2, utility weights were applied to the baseline mTDS score distribution for two weeks and to the post-treatment mTDS score distribution for weeks 3 through 24.

AEs were not considered in the model. The sponsor assumed that, as most AEs observed in the clinical trial (75% of patients had an AE deemed related to glycopyrrolate and 39% deemed related to placebo[3]) were of mild-to-moderate severity, patients would not require additional health care resources for their management. By doing so, the sponsor also assumed AEs had no impact on quality of life. Mortality was not included under the assumption that therapies for drooling would have no impact on length of life.

Only treatment acquisition costs were considered as the sponsor assumed that patients with neurologic conditions would already attend a number of physician visits and have tests performed to manage their condition within the modelled time horizon, thus further health care costs would not accrue. At $625 per 473 mL bottle of 1 mg/5 mL glycopyrrolate solution, the cost per mg is $6.6068. Given weight-based dosing for glycopyrrolate, the sponsor assumed patients were identical to the gender-weighted 50th percentile from WHO growth charts for Canada,[5,6] based on a mean age of nine years old and 63.9% male gender, consistent with the population studied in the randomized trial. Applying the mean daily dose of 0.15 mg/kg observed in the clinical trial (see Table 11 for further information on dosage) and assuming a 98.9% adherence rate as per patients who completed the trial, the weekly costs of glycopyrrolate treatment were calculated as $192.16, for a total treatment cost of $4,612 over the 24-week time horizon.

Sponsor's Base Case

In the sponsor's probabilistic base case, over a 24-week time horizon, the use of glycopyrrolate oral solution was associated with an incremental cost of $5,277 and an incremental QALY gain of 0.015, leading to an ICUR of $357,769 per QALY when compared to no treatment.

Table 2: Summary of Results of the Sponsor's Probabilistic Base Case

	Total costs ($)	Incremental cost ($)	Total QALYs	Incremental QALYs	Incremental cost per QALY
No treatment	0	–	0.186	–	357,769
Glycopyrrolate	5,277	5,277	0.206	0.015	

QALY = quality-adjusted life-year.

Source: Adapted from sponsor's pharmacoeconomic submission, Table 11.[2]

The sponsor also submitted a deterministic analysis, where the incremental cost of glycopyrrolate compared to no treatment was reported as $4,612 with a QALY gain of 0.021, resulting in an ICUR of $221,647 per QALY. Of note, the ICUR resulting from the probabilistic analysis was systematically around $135,000 per QALY higher than the result of the deterministic analysis.

Summary of Sponsor's Sensitivity Analyses

The sponsor conducted a series of deterministic one-way sensitivity analyses to explore the impact of changing assumptions within the model, including mean age of the children; mean daily dose of glycopyrrolate per kg of body weight; the disutility value associated with each point of change on the mTDS scale; mean patient weight; treatment adherence; patient's weight-for-age percentile; the utility value for an mTDS score of 1; and the percentage of patients who are male. Of these, analyses altering the amount of glycopyrrolate treatment given had the largest impact including: altering the mean age, mean patient weight, patient's weight-for-age percentile, the mean dose per kg assumed, and adherence percentage. Additionally, varying the disutility value associated with each point change along the mTDS score had a large impact on the estimated ICUR (see Table 14).

Limitations of Sponsor's Submission

Active comparators not considered: The sponsor excluded active comparators from the model as no other pharmaceutical agents are indicated for sialorrhea in Canada. However, according to the clinical expert consulted by CADTH, patients in the indicated population would likely receive oromotor and/or behavioural therapy, off-label botulinum toxin A injections, and/or oral surgery. Other patients may receive orally administered atropine or other anticholinergics. While CADTH was unable to assess the cost-effectiveness of glycopyrrolate relative to these comparators, the annual cost of onabotulinumtoxin A injections for sialorrhea was estimated to be approximately $990 to $2,200 per year, depending on the frequency of administration (see Table 16). Annual drug acquisition costs for anticholinergic medications used to treat sialorrhea can be found in Table 6, with off-label atropine drops costing $40 to $80 annually per patient, while off-label scopolamine (also known as hyoscine) patches would cost approximately $600 per year.

Model structure does not adequately reflect real-world outcomes: The sponsor oversimplified the clinical condition and the impact of treatment by using a decision tree. The conceptualization of a model should incorporate the potential for changes along the clinical or care pathway and be structured in a way to accommodate these changes.[8] In providing a decision tree structure with only a single transition point, the sponsor oversimplified real-world response to treatment. Despite evidence of patients gaining and losing response over time within the individual patient data of the randomized trial,[7] there were no subsequent opportunities for modelled patients to further improve or deteriorate beyond the single transition point at the second week of treatment. Rather, patients were assumed to remain in the same mTDS score from week 3 until the end of the model time horizon (week 24). Additionally, modelled patients could not stop therapy once started, regardless of whether such discontinuation was due to AEs, lack of efficacy, or no longer requiring treatment (e.g., having learned to swallow or switching to another therapy). The model may have been better represented with a Markov structure which would have allowed for patients to transition between health states with multiple opportunities for response to change and could have considered the impacts associated with treatment discontinuation. Finally, the mTDS scale has not been validated and thus its reliability as an efficacy outcome is uncertain (see Clinical Report, Appendix 4), although the FDA considered a three-point change in mTDS score to be clinically meaningful.[7] Due to the submitted model structure, CADTH was unable to address this limitation.

Insufficient time horizon: The 24-week time horizon is insufficient to demonstrate all costs, harms, and benefits associated with glycopyrrolate. Treatment for sialorrhea within the Health Canada indicated population would be chronic for many patients. According to the clinical expert consulted on this review, the 24-week time horizon is not adequate as the expected use of glycopyrrolate may extend beyond this time period. Data on long-term efficacy remains unknown as the pivotal trial was eight weeks in duration,[3] while the longest available non-randomized study was 24 weeks in duration.[9] The cost-effectiveness of glycopyrrolate over the potential full length of treatment and resulting downstream implications remains unknown. CADTH was unable to assess the examine the results over a longer time horizon.

Inappropriate efficacy time point: The beneficial effect of glycopyrrolate was assumed to occur at week 2 in the model, despite the sponsor's use of the week 8 distribution of mTDS scores in the Zeller trial to inform this model input.[3] This approach is inconsistent with the data available and overestimates treatment benefits. Mean mTDS scores reported in the trial indicated continuing improvement between week 2 and week 8, with most of the benefit in terms of the mean score having occurred by week 4.[3] CADTH reanalyses therefore considered the most relevant time point at which to apply treatment benefit to be at week 4, given the limitation of the model allowing for only a single transition point. Therefore, CADTH researchers applied the efficacy transition at week 4 and used the distribution of mTDS scores as measured in week 4 in the trial, in order to ensure consistency between the modelled results and the trial.[3] However, as week 4 was not the primary time point of the trial, a scenario analysis was conducted where the trial end point (week 8 or later) mTDS score distribution was applied within the model at week 8 (see Table 15).

Arbitrary incremental disutility: The utility value of never drooling (0.500 for an mTDS score of 1) was based on the utility reported for having a Gross Motor Function Classification System (GMFCS) Level II, which a NICE (UK) guideline committee on the assessment and management of CP in patients under 25 years of age deemed best representative of the quality of life of children and young people with CP who do not, or

rarely, drool.[4] Due to a lack of data on utility weights across the mTDS scale, NICE assigned an arbitrary disutility of 0.025 (5% of 0.500) per unit increase in score. The use of an arbitrary disutility increases uncertainty in the true magnitude of effect that improvements in drooling has on patient's quality of life. In the absence of other data, CADTH conducted sensitivity analyses around its base case assuming a disutility of 0.020 and 0.030 per mTDS point to explore the impact of varying this parameter.

Different baseline populations: The sponsor's model had patients start in different distributions based on mTDS score depending on which treatment they were assigned to within the Zeller trial. While consistent with baseline measures in the clinical trial,[3] in clinical practice, the decision to treat or not treat patients with glycopyrrolate would occur within the same population. CADTH reanalyses combined the baseline mTDS distributions for both arms of the study into a pooled distribution to reflect the expected distribution of baseline mTDS scores for a common population.

Age distribution: For the indicated population (i.e., patients three to 18 years of age), the sponsor assumed a uniform age distribution in the probabilistic analysis. While pediatric patients with neurologic conditions are equally likely to be any age, according to the clinical expert consulted by CADTH, those seeking pharmaceutical treatment for drooling are less likely to be on the youngest end of the indicated age range (as drooling may be viewed as acceptable among children in that age group, or they are seeking oromotor and/or behavioural therapy to learn to swallow), or at the oldest end of the indicated age range (as patients are more likely to have learned to swallow, have received surgery, or have grown to expect — or have caregivers who have grown to expect — drooling). Due to the sensitivity of the model to inputs that impact the amount of glycopyrrolate treatment received, it was noted that the uniform age distribution lead to the observed difference between the results of probabilistic and deterministic analyses, therefore, CADTH reviewers examined the ages of patients within the clinical trial[3] and assigned a gamma distribution based on the mean age of 9.42 years with a standard deviation of 3.92 years. Probabilistic age draws were then rounded to the nearest year and weight was estimated using Canadian growth charts,[5,6] with drawn ages outside of the indicated age range of three to 18 excluded. Due to the increased costs of treating older and thus heavier patients, this change lowered the probabilistic ICUR closer to the findings of the sponsor's deterministic base-case analysis.

Patient weight overestimated: While the sponsor's decision to use the median (i.e., 50th percentile) weight-for-age found within the general population of children in Canada[5,6] was conservative, patients in the Zeller trial had a mean weight-for-age percentile between the 21st and 30th percentile on WHO growth charts for Canada and a median weight-for-age consistent with the 10th percentile.[7] According to the clinical expert consulted by CADTH, it is common for children with neurologic conditions such as CP to weigh less than other children of their age, and CADTH assumed the patient population would have weights consistent with the 25th percentile of WHO growth charts for Canada.

AEs not included: Although 20% of patients in the glycopyrrolate group within the Zeller trial[3] had at least one severe AE compared to none in the placebo group, the sponsor did not consider the impact of treatment-emergent AEs on costs or quality of life within the model. The most commonly reported AEs experienced by patients in the trial were dry mouth, constipation, vomiting, nasal congestion, flushing, and urinary retention, all of which occurred more frequently in the glycopyrrolate group than in the placebo group. The sponsor's base-case results indicated that there was a small incremental quality of life benefit associated with glycopyrrolate (i.e., 0.015 QALYs in the sponsor's base case which

can be interpreted as five additional days of perfect health), however, it is difficult to tell how these results might be affected by the inclusion of AEs. The potential quality of life impacts from these AEs raises substantial uncertainty to the expected clinical benefits modelled for glycopyrrolate within the sponsor's model, especially given the already small QALY benefits associated with glycopyrrolate. CADTH was unable to address the impact of AEs in the model due to structural constraints with the sponsor's model.

Inappropriate evaluation of parameter uncertainty: While the sponsor conducted a probabilistic analysis to account for variation within the included efficacy, utility, and patient characteristic parameters, almost all parameters were bounded by an arbitrary coefficient of 25% around the mean. The sponsor did not provide justification for this assumption. The use of an arbitrary coefficient rather than true measures of variance around each mean decreases the likelihood that the model captures the true nature of uncertainty within the parameters. CADTH did not address this limitation and the uncertainty observed in the probabilistic results may therefore not fully reflect the true uncertainty around model parameters.

CADTH Reanalyses

While several limitations with the sponsor's submission could not be addressed in reanalyses (model structure, time horizon, lack of active comparators, arbitrary definition of uncertainty), other limitations could be explored by CADTH, including:

1. changing the treatment-benefit time point and patient mTDS score distribution, as reported from the trial, to occur consistently at week 4
2. combining the baseline trial mTDS score into a single pooled distribution to more appropriately model the introduction of glycopyrrolate into a single population
3. altering the age distribution to be more reflective of patients within the trial, as not all indicated ages are equally likely to be treated for drooling with a pharmacological agent
4. using the 25th percentile of WHO weight-for-age growth charts to calculate weight, as the trial population is consistent with expert input that children with neurologic conditions like CP are usually smaller than the general population of children at that for age.

The results from these step-wise analyses can be found in Table 3, culminating in a CADTH base case which found that glycopyrrolate was associated with 0.013 additional QALYs at an additional cost of $3,884, for an ICUR of $292,274 per QALY. The model was found to be most sensitive to changes that impacted the amount of glycopyrrolate treatment received (i.e., patient age and body weight percentile for age).

Scenario analyses exploring the effect of varying the incremental disutility associated with each point of mTDS score, as well as the impact of applying the final mTDS score distribution from the trial to week 8 within the model, can be found in Table 15 of Appendix 5.

Table 3: CADTH Base-Case Reanalyses

	Description	Sponsor's base case value	CDR value	Incremental cost ($)	Incremental QALYs	ICUR ($/QALY)
	Sponsor's base case	**Reference**		**5,277**	**0.015**	**357,769**
1	Transition point for efficacy (post-treatment mTDS score distribution)	8-week post-treatment mTDS distribution from trial begins at week 2	Week 4 post-treatment mTDS distribution from trial begins at Week 4	5,323	0.011	482,989
2	Baseline population	Baseline mTDS distributions reflect trial population at baseline, separated by treatment group	Baseline mTDS distribution reflects combined trial population at baseline	5,296	0.016	340,453
3	Distribution for patient age	A uniform distribution was assumed for age, range: 3 to 18 years	Age is a gamma distribution around trial's mean and SD, limited to range of 3 to 18 years	4,458	0.015	307,139
4	Body weight percentile for age	Weight at 50th percentile of WHO growth chart	Weight at 25th percentile of WHO growth chart	4,665	0.014	327,759
1 to 4	**CADTH base case**			**3,884**	**0.013**	**292,274**

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility analysis; mTDS = modified Teacher's Drooling Scale; QALY = quality-adjusted life-year; SD = standard deviation.

In order to be considered cost-effective at a WTP threshold of $50,000 per QALY, the price of glycopyrrolate would need to be reduced by 83% under CADTH's base case (see Table 4).

Table 4: CDR Reanalysis Price Reduction Scenarios

ICURs of glycopyrrolate versus no treatment		
Price	**Base-case analysis submitted by sponsor ($)**	**Reanalysis by CDR ($)**
Submitted	357,769	292,274
10% reduction	323,427	266,235
20% reduction	289,034	240,248
30% reduction	256,271	195,753
40% reduction	217,491	172,013
50% reduction	178,481	146,559
60% reduction	148,235	115,849
70% reduction	107,479	85,987
80% reduction	71,712	58,859
90% reduction	36,629	29,005

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

Issues for Consideration

Other available glycopyrrolate formulations: Health Canada stipulates that compounding of pharmaceuticals should only occur if there is a lack of product availability and not solely for economic reasons.[10] As glycopyrrolate oral solution (Cuvposa) is now available, compounded glycopyrrolate injection or powder was not considered an appropriate comparator for this review, however, some off-label usage may continue to occur. The costs paid by the public drug plans for compounded glycopyrrolate oral solution are not publicly available.

Use in the adult population: Although glycopyrrolate is indicated for children three to 18 years of age, according the clinical expert consulted by CADTH a teenage patient who is seeing beneficial effect is likely to continue taking it into their adult years. The cost of using glycopyrrolate for an adult patient weighting 60 kg would be between $8,681 and $43,406 per year, depending on dose level (see Table 11).

Patient Input

No patient group input was received for this review.

Conclusions

After attempting to address several limitations with the sponsor's analysis, where possible, CADTH's base case ICUR for glycopyrrolate compared with no treatment was $292,274 per QALY; a price reduction of 83% would be required in order for glycopyrrolate to be considered cost-effective at a WTP of $50,000 per QALY.

However, a number of larger issues remain which could not be addressed in reanalysis, including the oversimplification of the condition and treatment response; the lack of consideration of treatment discontinuation; the lack of comparison to current standard of care or any active comparator; the arbitrary nature of the health utility values assigned to an unvalidated efficacy outcome; and the exclusion of AEs associated with glycopyrrolate from consideration within the model. Additionally, the effects of glycopyrrolate beyond 24 weeks are uncertain and no estimate of cost-effectiveness over a longer time period is possible. As such, the true cost-effectiveness of glycopyrrolate is unknown.

Appendix 1: Cost Comparison

The comparators presented in Table 5 were deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in Table 5 and as such may not represent the actual costs to public drug plans. Indicated comparators are listed in Table 5, while comparators used off-label are listed in Table 6.

Table 5: CADTH Cost Comparison Table for Prescription Drugs Indicated for Pediatric Patients With Sialorrhea

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dose	Average daily drug cost ($)	Average annual drug cost ($)
Anticholinergics						
Glycopyrrolate (Cuvposa)	1 mg/5 mL	Solution in 473 mL bottle	$625.0000[a]	Dosing level 1 (~0.02 mg/kg) to dosing level 5 (~0.1 mg/kg) orally three times daily	**13 kg patient** 5.15 to 25.76 **30 kg patient** 11.98 to 59.46 **48 kg patient** 19.02 to 95.14	**13 kg patient** 1,881 to 9,405 **30 kg patient** 4,341 to 21,703 **48 kg patient** 6,945 to 34,725

Note: All prices are from the Ontario Drug Benefit Formulary[13] (accessed July 2019) unless otherwise indicated and do not include dispensing fees or administration. One year was assumed to be 365 days.

[a] Sponsor-submitted price.[2]

Table 6: CADTH Cost Comparison Table for Treatments Used Off-label for Pediatric Patients With Sialorrhea

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dose	Average daily drug cost ($)	Average annual drug cost ($)
Botulinum Toxins						
Abobotulinumtoxin A (Dysport)	300 U/Vial 500 U/Vial	Powder for solution	$385.0000 $642.0000	100 to 140 units[a]	Every 3 months: $4.22 Every 6 months: $2.11	Every 3 months: $1,540 Every 6 months: $770
Onabotulinumtoxin A (Botox)	50U/Vial 100U/Vial 200U/Vial	Powder for solution	$178.5000 $357.0000 $714.0000	70 units[b]	Every 3 months: $3.91 Every 6 months: $1.96	Every 3 months: $1,428 Every 6 months: $714
Anticholinergics						
Atropine sulphate	1%	Ophthalmic solution	$0.7320 per mL	10 to 19 kg: 1 drop, three times daily[c] ≥ 20 kg, 2 drops, three times daily[c]	13 kg: $0.11 30 kg: $0.22 ≥ 48 kg: $0.22	13 kg: $40 30 kg: $80 ≥ 48 kg: $80

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dose	Average daily drug cost ($)	Average annual drug cost ($)
Benztropine mesylate	1 mg	Tablet	$0.0522	3.8 mg/day (range = 0.5mg to 6mg)[d]	$0.03 to $0.31	$10 to $114
Scopolamine[e] (Transderm-V)	1.5 mg	Transdermal patch/disc	$4.9300[e]	Maintenance dose after 4 weeks: 1 patch every 3 days[f]	$1.64	$600
Trihexyphenidyl hydrochloride	2 mg	Tablet	$0.0376	0.095 mg/kg/day twice daily in equally divided doses[g]	13 kg: $0.05 30 kg: $0.11 ≥ 48 kg: $0.17	13 kg: $16.95 30 kg: $39.11 ≥ 48kg: $62.58

RCT = randomized controlled trial.

Note: All prices are from the Ontario Drug Benefit Formulary[13] (accessed July 2019) unless otherwise indicated, and do not include dispensing fees or administration. One year was assumed to be 365 days.

[a] Based on a systematic review by Rodwell et al.[14] citing an RCT by Alrefai et al.[15] Costing based on 100 U for all weights. Booster dose was assumed to continue every three to six months. The initial dose used in the study was 100 U; subsequent dose was 140 U. Cost per treatment includes wastage of excess medication in vials.

[b] Based on a systematic review by Rodwell et al.[14] The dose of Botox varied across included studies; the median total dose of Botox injected was 70 U (10 U to 100 U). The median total dose per gland of Botox was 25 U (5 U to 25 U) or 2 U/kg, as reported by studies that provided this information. Cost per treatment includes wastage of excess medication in vials.

[c] Based on a study by Scofano Dias et al.,[16] where ophthalmic drops of 0.5% were used. Weight-based dosing was applied (minimum 10 kg to 19 kg, to ≥ 20 kg). Assumes drops of 1% will be used in the same regimen as 0.5% drops; 20 drops per mL assumed.

[d] Based on a study by Camp-Bruno et al.[17]

[e] Pricing based on Saskatchewan Drug Formulary[19] (accessed July 2019). Scopolamine is another term for hyoscine.

[f] Based on Parr et al.,[20] where treatment regimen is distributed as follows: week 1: ¼ patch; week 2: ½ patch; week 3: ¾ patch; week 4: full patch, and patch is replaced every three days.

[g] Based on a study by Carranza-del Rio et al.,[18] with a mean initial dose of 0.095 mg/kg per day (range = 0.01 mg/kg per day to 0.414 mg/kg per day).

Appendix 2: Summary of Key Outcomes

Table 7: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is Glycopyrrolate Relative to No Treatment?

Glycopyrrolate vs. no treatment	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Sponsor's base case: $357,769 per QALY CADTH base case: $292,274 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.

Appendix 3: Additional Information

Table 8: Submission Quality

	Yes/ good	Somewhat/ average	No/ poor
Are the methods and analysis clear and transparent?	X		
Comments Reviewer to provide comments if checking “no”	None		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	None		

Table 9: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CADTH

☐ Adaptation of global model/Canadian model done by the sponsor

☐ Adaptation of global model/Canadian model done by a private consultant contracted by the sponsor

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the sponsor

☒ Other (please specify): De novo model

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

Sialorrhö, a different formulation than that approved in Canada, consisting of 400 mg/mL of glycopyrronium bromide, was reviewed by the Institute for Quality and Efficiency in Health Care (IQWiG, Germany) for uncontrolled salivation in children and adolescents with chronic neurologic disorders such as CP.[21] No English summary was available; however, it was determined that there was no added benefit and the drug was not listed. In July 2017, The Scottish Medicines Consortium (SMC, Scotland) accepted Sialanar, 400 mg/mL of glycopyrronium bromide, to be used for the treatment of drooling in children and adolescents three years of age and older with chronic neurologic disorders.[22] Glycopyrrolate (Cuvposa) is currently under review by the Institut national d'excellence en santé et en services sociaux (INESSS, Quebec)[23] under its Health Canada–approved indication.

Appendix 5: Reviewer Worksheets

Sponsor's Model Structure

The sponsor submitted a probabilistic cost-utility analysis, in the form of a decision tree, comparing glycopyrrolate oral solution to no treatment for the treatment of chronic severe drooling in children with neurologic conditions (e.g., CP), from the perspective of the Canadian health care system. The time horizon was 24 weeks with no discounting applied to costs and effects.

Patients in each group entered the model in a distribution based on mTDS scores consistent with the scores observed at baseline in the Zeller trial for that group,[3] which ranged from 1 (dry, never drools) to 9 (profuse drooling). The model allowed for a single transition in mTDS score at two weeks, which was based on the mTDS score distribution observed in the clinical trial efficacy assessment at eight weeks[3] (see Table 10). No further improvement or deterioration in score was possible after this transition.

Table 10: Sponsor's Model Distributions and Utility Weights by Severity of Drooling

mTDS score	Baseline distribution[a]		Post-transition distribution[b]		Utility value
	Glycopyrrolate	Placebo or no treatment	Glycopyrrolate	Placebo or no treatment	
1 = Dry: never drools	0%	0%	0%	6.7%	0.500
2 = Mild: only the lips are wet, occasionally	5.9%	13.3%	41.2%	0%	0.475
3 = Mild: only the lips are wet, frequently	11.8%	6.7%	35.3%	13.3%	0.450
4 = Moderate: wet on the lips and chin, occasionally	5.9%	13.3%	17.6%	26.7%	0.425
5 = Moderate: wet on the lips and chin, frequently	0%	13.3%	5.9%	13.3%	0.400
6 = Severe: drools to the extent that clothing becomes damp, occasionally	11.8%	6.7%	0%	6.7%	0.375
7 = Severe: drools to the extent that clothing becomes damp, frequently	23.5%	26.7%	0%	26.7%	0.350
8 = Profuse: clothing, hands, tray, and objects become wet, occasionally	0%	0%	0%	6.7%	0.325
9 = Profuse: clothing, hands, tray, and objects become wet, frequently	41.2%	20.0%	0%	0%	0.300

mTDS = modified Teacher's Drooling Scale.

[a] Based on the last non-missing score before the start of study drug administration.

[b] Based on the rounded average of the available values recorded at visit 8.

Table 11: Detailed Dosing Recommendations for Glycopyrrolate Oral Solution

Weight (kg)	Dose level 1 (mg)	Dose level 2 (mg)	Dose level 3 (mg)	Dose level 4 (mg)	Dose level 5 (mg)
13 to 17	0.3	0.6	0.9	1.2	1.5
18 to 22	0.4	0.8	1.2	1.6	2.0
23 to 27	0.5	1.0	1.5	2.0	2.5
38 to 32	0.6	1.2	1.8	2.4	3.0
33 to 37	0.7	1.4	2.1	2.8	3.0
38 to 42	0.8	1.6	2.4	3.0	3.0
43 to 47	0.9	1.8	2.7	3.0	3.0
≥ 48	1.0	2.0	3.0	3.0	3.0

Source: Cuvposa Product Monograph.[1]

Table 12: Data Sources

Data input	Description of data source	Comment
Baseline characteristics	Information on mean age, sex proportion, average weight, and average daily dose were obtained from the pivotal clinical study (Zeller trial).[3]	Minor inconsistencies. The mean age in the model is slightly lower than the reported mean age in Zeller et al. (8-week phase III trial), in which the modelled population's baseline characteristics were based on 9 years in the submitted model vs. 9.4 years for the weighted average age in the trial. Assumptions about the distribution of age is a key model driver. Uniform distribution between ages 3 and 19 years is not appropriate; see Limitations of the Sponsor's Submission in the main report for details.
Efficacy	Distribution of patients in each treatment group across mTDS scores 1 through 9 based on 8-week placebo-controlled RCT to estimate the relative efficacy of glycopyrrolate compared to placebo.[3]	Inappropriate to assume that a clinical benefit observed at week 8 would begin at week 2 (see Limitations of the Sponsor's Submission in the main report for details). Model does not allow for mTDS score to change after the initial response at week 2. In other words, no further improvement or deterioration in mTDS score would be possible after week 2 (see Limitations of the Sponsor's Submission in the main report for details).
Natural history	Treatment with glycopyrrolate is not assumed to affect underlying neurologic condition with the exception of drooling, especially in terms of progression and mortality. Placebo arm of the Zeller trial reflected the no treatment comparator in the model.[3]	Appropriate. Patients assigned to placebo in the pivotal study[3] also improved in drooling score, although to a lesser extent than the active treatment group. As no data exist on a population randomized to no treatment, it is not possible to determine whether the observed effect is either a true placebo response, an improvement due to more frequent interaction with health care providers, or regression toward the mean. Thus, using the placebo group data to represent patients not receiving treatment is deemed acceptable.

Data input	Description of data source	Comment
Utilities	Utility scores were taken from those derived in a 2017 NICE Guideline Cerebral Palsy in under 25s: assessment and management, Appendix G – Health Economics.[4]	Highly uncertain. The utility decrement of 0.025 between mTDS score units was chosen arbitrarily to reflect an assumed linear relationship between drooling and quality of life; therefore, a disutility of 0.025 was applied per unit increase in the mTDS score, starting with 0.5 at an mTDS score = 1 and ending with 0.3 at an mTDS score = 9. In the absence of utility data to appropriately quantify the quality of life of different severe drooling health states, the utility difference between an mTDS score of 1 and 9 was compared to the difference in the physical health summary score of a different outcome measure as a way to validate the change in quality of life from a non-drooling state of mTDS = 1 and profusely drooling state of mTDS = 9.[4] This is likely imprecise and this approach has not been formally validated.
Adverse events	Not considered	Inappropriate. Given the very small incremental change in QALYs between the treatment and no treatment strategies within the model, the exclusion of adverse events may overestimate the expected clinical benefits of treatment (see Limitations of the Sponsor's Submission within the main report).
Resource Use and Costs		
Drug	Sponsor-submitted prices; dosing regimen was based on Product Monograph.	Appropriate
Administration	None.	Acceptable as glycopyrrolate is an oral solution that does not require specialized knowledge to administer.
Adverse events	Costs of adverse events related to medication use were not considered in this analysis.	Inappropriate. A greater proportion of patients on glycopyrrolate in clinical trial had adverse events, including serious adverse events.

mTDS = modified Teacher's Drooling Scale; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial; vs. = versus.

Table 13: Sponsor's Key Assumptions

Assumption	Comment
Treatment effect was assumed to start at 2 weeks	Inappropriate. The Zeller trial (pivotal study) reported that 52.6% of patients on glycopyrrolate had responded by week 2 and 73.7% of patients had responded by week 8. Assigning the week 8 mTDS distribution at week 2 overestimates the beneficial effect of glycopyrrolate.
Efficacy data at 8 weeks were extended to 24 weeks assuming no deterioration or improvement following the 8-week assessment	This assumption is based on the 24-week open-label study[3], where 52.7% of patients had responded by week 8, 56.7% by week 16, and 52.3% responding at week 24.[9] However, given the limited number of patients studied, it is unclear whether the proportion responding to treatment would be similar in the longer term.
Discontinuation was not explicitly included in the model	Inappropriate, as several patients had discontinued therapy within the 8-week randomized trial.[7] The impacts of treatment discontinuation were not modelled.

Sponsor's Results

Results of the sponsor's one-way sensitivity analyses are presented in Table 14.

Table 14: Sponsor's Deterministic One-Way Sensitivity Analyses

Parameter	Base case	Lower bound	ICUR	Upper bound	ICUR ($)
Sponsor's base case					221,647
Main daily glycopyrrolate dose (mg/kg), range from 24-week trial[9]	0.15	0.10	147,764	0.30	443,293
Percentage male, (±25%)	63.9%	47.9%	221,647	79.9%	221,647
Mean age of patients (years), range from 24-week trial [9]	9	3	112,275	18	503,993
Mean weight of patients (kg), (±25%)	28	21	166,235	35	224,047
Adherence to treatment, (±25%)	98.9%	74.2%	166,235	100%	224,047
Disutility value per mTDS score increase, (±25%)	0.025	0.019	295,529	0.031	177,317
Utility value for children with mTDS score of 1, (±25%)	0.500	0.375	221,647	0.625	221,647
Percentile weight-for-age	50th	25th	190,924	75th	239,052

ICUR = incremental cost-utility ratio; mTDS = modified Teacher's Drooling Scale.

Source: Adapted from Cuvposa Pharmacoeconomic Submission, Table 8, and Figure 10.[2]

CADTH Reanalyses

CADTH's base-case analysis is outlined in Table 3. Scenario analyses exploring uncertainty in the base case can be found in Table 15. The model remains sensitive to the time point of efficacy benefit and the choice of disutility per point along the mTDS scale.

Table 15: CADTH Scenario Analyses Around the Base Case

	Description	CADTH base-case value	Scenario value	Incremental cost ($)	Incremental QALYs	ICUR ($/QALY)
	CADTH base case			**3,884**	**0.013**	**292,274**
A	Trial end point mTDS score data (i.e., post-treatment distributions from sponsor's base case) are applied at week 8	4-week post-treatment distributions from trial, applied at week 4	8-week post-treatment distributions from trial, applied at week 8	3,848	0.011	334,618
B	Increased disutility per point of mTDS score	0.025	0.030	3,858	0.016	242,168
C	Decreased disutility per point of mTDS score	0.025	0.020	3,870	0.011	364,867

ICUR = incremental cost-utility analysis; mTDS = modified Teacher's Drooling Scale; QALY = quality-adjusted life-year.

Although CADTH was not able to include onabotulinumtoxin A as a comparator in the model, the annual cost of therapy has been estimated as approximately $990 to $2,200 per patient, per year (see Table 16).

Table 16: Cost of Botulinum Toxin Therapy if Used Off-Label for Sialorrhea

Item	Cost	Source
Drug acquisition cost, onabotulinumtoxin A, 100 unit vial	$357.00	ODB Formulary[11]
Botulinum toxin injection for the treatment of sialorrhea (unilateral or bilateral)	$50.00	Ontario Schedule of Benefits for Physicians Services, G874[24]
Ultrasound guidance for botulinum toxin injection, for two or more injections	$28.10	Ontario Schedule of Benefits for Physicians Services, G880[24]
Sedation	$60.04 to 120.08	Ontario Schedule of Benefits for Physicians Services, 4 to 8 basic anesthesiologist units assumed on basis of other described procedures ($15.01 per unit)[24]
Total cost per procedure	$495 to $555	
Total annual cost	**$990 to $1,110 if every six months $1,981 to $2,221 if every three months**	

ODB = Ontario Drug Benefit.

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